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THE OPTIMISATION OF INTENSIVE TREATMENT STRATEGIES IN EARLY RHEUMATOID ARTHRITIS

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List of abbreviations

ACPA	Anti-Citrullinated Peptide-Antibody
ACR	American College of Rheumatologists
AE	Adverse Event
ANOVA	Analyses Of Variance
APC	Antigen Presenting Cell
ASPIRE	Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset
AUC	Area Under the Curve
BEST	Behandel Strategieën
CAMERA	Computer-Assisted Management in Early Rheumatoid Arthritis
CARDERA	Combination Anti-Rheumatic Drugs in Early RA
CareRA	Care in Early RA
CDAI	Clinical Disease Activity Index
CTLA4	Cytotoxic T lymphocyte-associated Antigen 4
COBRA	Combinatie Therapie bij Rheumatoïde Arthritis
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRP	C-Reactive Protein
DAS	Disease Activity Scores
DAS28(CRP)	DAS based on an algorithm of the 28 tender and swollen joint counts, the C-Reactive Protein status and the global health as estimated by the patient on a VAS scale
DMARD	Disease-modifying anti-rheumatic drug
EC	Ethics Committee
eRA	early Rheumatoid Arthritis
ESPOIR	Etude et Suivi des POlyarthrites Indifférenciées Récentes
ESR	Erythrocyte Sedimentation Rate
ETRA	Patients with Early Treatment (total delay ≤ 12 weeks)
EULAR	European League Against Rheumatism
GC	Glucocorticoid
GEE	Generalized Estimating Equation
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HCP	Healthcare Professional

HCQ	Hydroxychloroquine
HLA	Human Leucocyte Antigen
ICTS	Initial DMARD Combination Therapy with Steroids
IgG	Immunoglobulin G
IL	Interleukin
IMPROVED	Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease
IMT	Initial DMARD Monotherapy
IQR	Interquartile Range
ITT	Intention To Treat
IWT	Instituut voor Innovatie door Wetenschap en Techniek
JAK	Janus Kinase
LEF	Leflunomide
LTRA	Patients with Late Treatment (total delay > 12 weeks)
MTX	Methotrexate
NICE	National Institute for Health and Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
PGA	Patient's Global Assessment
PhGA	Physician's Global Assessment
PP	Per Protocol
PROMPT	Probable Rheumatoid Arthritis: Methotrexate versus Placebo Treatment
PTPN22	Protein Tyrosine Phosphatase, Non-receptor Type 22
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RF	Rheumatoid Factor
ROC	Receiver Operating Characteristic
RRP	Rapid Radiographic Progression
SD	Standard Deviation
SJC	Swollen Joint Count
SONORA	Study of New Onset Rheumatoid Arthritis
SPSS	Statistical Package for the Social Sciences
SSZ	Sulphasalazine
SvdH/SvH	Sharp/van der Heijde
SWEFOT	Swedish Farmacotherapy
TC	Tight Control

TEAR	Treatment of Early Aggressive Rheumatoid Arthritis
TICORA	Tight Control for Rheumatoid Arthritis
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
tREACH	Treatment in the Rotterdam Early Arthritis Cohort (tREACH)
TSS	Total Sharp Score
TSU	Tight Step Up
UA	Undifferentiated Arthritis
UZL	University Hospitals Leuven
VAS	Visual Analogue Scale
W	Week

Introduction

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What is Rheumatoid Arthritis?

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, generally affecting the peripheral joints with a poly-articular distribution. The acute features of this disorder are painful, swollen and stiff joints, but it may include also systemic manifestations in organs other than the joint. Moreover, the role of fatigue as an RA related symptom is quite prominent, especially in established RA. This disease has a worldwide prevalence in adults ranging between 0.2 to 1.0 percent, with a higher prevalence in more developed countries. Exact population numbers for Belgium are unknown, although it is estimated that approximately 80 000 individuals are affected. The peak age of RA onset is situated in the fifth decade. Furthermore, the disease is three times more common in women than in men. [1, 2]

Left insufficiently treated, RA can lead to bone and cartilage destruction, to loss of physical function and impairment of quality of life and participation. However, the course of disease is different per individual and hard to predict. Traditionally also an increase in morbidity and mortality is associated with RA. [3] Yet, a recent study demonstrated a decrease in excess mortality over time in patients with RA compared with the general population. [4] The frequency of comorbidities ranges between 25-60%, depending on the type of study, the type of evaluated comorbidity and the geographical region. Typical comorbidities cited are cardiovascular problems, infections and malignancy. Aside of these conditions, RA can also have an important psychological impact, with symptoms of anxiety and depression[5]. By consequence, often patients with RA have difficulties to participate actively in family life and social activities. Hence, management of RA should not only focus on the disease itself, but also on managing the frequent comorbidities and the mental and social wellbeing of the patient. [6]

Overlooking the description of this chronic condition above, it is not surprising that the management of RA generates high healthcare related and socioeconomic costs. Moreover, on top of these high medical costs, many patients with RA are hit by work loss and reduced productivity, not only affecting individual but also societal expenditures. [7]

The etiology of Rheumatoid Arthritis

Although the exact pathogenesis of RA is not yet completely unraveled, genetic and environmental aspects have been comprehensively investigated, giving rise to an improved understanding of the dysregulation of the immune system involved in RA. [2]

It is estimated based on evidence from twin studies that over 50% of the risk for the development of RA can be attributed to genetic factors. [8, 9] Patients with RA more frequently have relatives with RA or other immune-mediated disorders.

Until recently, only few genetic risk factors for RA have been identified. [10] The first genetic risk factor is the human leucocyte antigens (HLA) region which seems at the moment the most significant genetic region linked to RA. The HLA molecules are encoded by the major histocompatibility complex on chromosome 6 region 6p21.31 for RA. These molecules are expressed on the surface of antigen presenting cells (APCs), activating the T-cells of the immune system. Most HLA-DR alleles with an increased risk for RA susceptibility have a common amino acid motif, the so-called ‘shared epitope’, in the β chain of the HLA-DR molecules. [11, 12] Most research in this field is performed on Caucasian populations and slight differences in this genotypic background in other ethnicities seems to lead to less severe phenotypes. [13, 14]

Another well studied genetic risk factor for RA is protein tyrosine phosphatase, non-receptor type 22 (PTPN22). The tyrosine phosphatase coded by this gene affects the responsiveness of the T- and B-cell receptors. Hence, mutations in PTPN22 can be related to an increased risk of RA. [15]

A last genetic risk factor we discuss in this introduction is cytotoxic the T lymphocyte-associated antigen 4 (CTLA4). CTLA4 codes is a protein receptor on the surface of T-cells and can act as a down regulator of the immune system, which makes it a prime target in auto immune diseases. [15] Nowadays, genome wide association studies identify constantly new genetic regions related to RA, although the modest effects of these individual loci limit the use of all these genetic risk factors in daily clinical practice. [10]

Being an autoimmune disease, RA can be characterized in most cases by the production of autoantibodies. Rheumatoid Factor (RF) and Anti-Citrullinated Peptide-Antibodies (ACPA) are until now the most important autoantibodies in RA detection, diagnosis and research. [16]

RF is an immunoglobulin type M, directed against the Fc component of immunoglobulin G (IgG). Lymphocytes secreting RF are present in the peripheral blood, synovial fluids and bone marrow in patients with RA. [17] The immune complexes formed by RF and IgG activate the immune system. Macrophages are activated, releasing pro-inflammatory cytokines like tumor necrosis factor (TNF) and interleukins (ILs). On their turn, these proteins enhance the production of cartilage- and bone-destructive molecules and the release of other pro-inflammatory cytokines.

ACPA, historically also called anti-keratin antibodies or anti-perinuclear factor, are increasingly important autoantibodies. The ACPA-producing B-lymphocytes and the target of ACPA, citrullinated proteins are present in the synovial tissue and fluids of patients with RA. Immune complex formation again activates macrophages leading to the production of TNFs and ILs. A close link is found between the presence of HLA-DR shared epitope and an increase in ACPA-production.

RF and ACPA are the two most-used markers for the detection and diagnosis of RA. Both proteins show similar sensitivity but RF tends to be less specific for RA. Detecting and diagnosing RA is improved by measuring both autoantibodies, although it is to be noted that neither RF nor ACPA are decisive in the diagnosis of RA. [18]

In addition to ACPA and RF, anti-carbamylated protein antibodies recently appear to be a promising target in RA research. These antibodies are associated with the future onset of RA and with increased disease severity in early RA [19-21].

Aside of genetic variations, environmental risk factors can also increase the risk of developing RA. The most established risk factor is smoking. It doubles the risk of developing RA but this effect seems restricted to patients who are ACPA positive. There seems to be a strong relationship between smoking, ACPA and the HLA-DR risk allele. [22] Alcohol intake, coffee intake, vitamin D status, oral contraceptive use, and low socioeconomic status are other suspected risk factors, although decisive evidence is lacking. [23]

Seeing the evidence above, RA can be seen more as a clinical syndrome than as one specific disease. Different genetic and environmental risk factors are at the basis of different RA subsets with distinct cellular and subcellular pathophysiological backgrounds, all converging to a similar type of dysregulation of the biological homeostasis, leading to RA as a clinical syndrome. This hypothesis can explain the variations in disease course between patients with RA and the failure of certain anti-rheumatics in individual patients.

Clinical Assessment of Rheumatoid Arthritis

The hallmark of RA, joint inflammation, is also the focus of clinical assessment in RA. [24] Nowadays, swollen and tender joint counts should systematically be performed in daily clinical practice. The standard joint count in trials focuses on 28 joints in the knees, upper limbs and hands and might be used also in clinical practice. An important issue is that the feet are neglected in this limited joint count. Therefore, physicians might prefer total joint counts, including the feet,

specifically in daily practice. Additionally, serum inflammation markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) status should regularly be measured. Furthermore, the patient is sometimes asked on a scale to rate his perceived global health, his pain level and his fatigue level on a visual analogue scale (VAS) ranging from 0 to 100. The physician can also give his estimation of the patient's global health on a VAS scale. [24] Another important and widely used measure is the health assessment questionnaire (HAQ), which gives an idea of the patient's physical function. [1, 24, 25]

In the late nineties, some of the measurements mentioned above were grouped to give a general appraisal of disease activity status or treatment response [26]. Such Disease Activity Scores (DAS), combining joint counts, serum inflammation markers and the patient's estimation of his/her global health or his/her disease activity are now routinely used in daily practice. [27] New disease activity measures were developed such as the clinical disease activity index (CDAI) the SDAI and the 2010 Boolean remission criteria of the American College of Rheumatologists (ACR). [28] Limitations of these scores are the use of the 28 joint count - hence without counting swelling and pain in the lower limbs - in some of the disease algorithms and the use of ESR of CRP status, which are not always readily available in daily practice.

Diagnosis of a patient with RA is left to the discretion of the rheumatologist. However, classification criteria were developed to aid the physician in this challenging task. These criteria are based on the characteristics of RA as mentioned above. The first criteria distinguished between a more established RA and other types of established musculoskeletal disorders. [29, 30] However, these criteria have difficulty identifying very early rheumatoid arthritis. Erosive joint damage and extra-articular disease, two ACR 1987 criteria, are for example more frequent in established RA and can be prevented by current treatment possibilities. Hence in 2010, the ACR and European League Against Rheumatism (EULAR) constructed new criteria, facilitating the classification of patients with a more early form of RA. [31]

How to treat Rheumatoid Arthritis?

A little history

Only a century ago, no effective treatment for RA existed. Patients suffered pain and discomfort on a daily base and could only hope that one day something effective could aid them. In such conditions, quack remedies are prone to develop. It just shows how desperate people are when being confronted with a disabling disorder as RA. These 'cures and treatments' for RA range from reasonable actions such as a diet and anti-infectious agents to more remarkable steps taken such as standing inside the carcass of a whale as witnessed on the coasts of Australia, applying an obscure sort of oil, secreted by the earthworm as seen in Scotland to even electric convulsion therapy in some cases. Placebo effect of course played a major role in the perceived efficacy of such remedies. [32] However, it is in these circumstances that the first seeds of effective RA treatment were planted. For example, gold salts were introduced in RA treatment around 1930 because it was believed that tuberculosis and other infectious diseases were potentially the cause of RA and gold was fairly effective in tuberculous disease. Hence, a false hypothesis could render a good result. Furthermore, in the 1950 glucocorticoids (GCs) made their appearance in RA treatment. Stress was than seen as a possible cause for RA and patients were prescribed stays at spas and other stress-relieving therapies. It was then believed that anti-stress treatments were successful because of adrenocortical stimulation and increase in GCs production. Hence, synthetic GCs were developed and they proved indeed very successful for RA treatment. Unfortunately GC's were given initially in dosages of 300mg/day, leading rapidly to severe adverse events and giving rise to their infamous reputation until today. Moreover, sometimes the discovery of a drug is helped by careful patient observation. Anecdotal reports in the South Pacific war stage in World War II described the improvement of RA symptoms in Allied soldiers on long-term anti-malarial therapy. Hence, chloroquine and hydroxychloroquine were introduced in the treatment of RA. As a side note, these anti-malarial agents originate from the 'fever tree' in South

America and this tree was already found to be a miraculous remedy for many diseases in the era of the Inca's. [33]

This very short and incomplete history illustrates the difficulty physicians had treating RA patients without many means. However, it is in this period that the first steps towards an effective RA treatment were taken. [32, 33]

Pharmacological treatments for RA

Today, patients with RA have fortunately access to more effective treatment options. For symptomatic treatment of RA, non-steroidal anti-inflammatory drugs (NSAIDs) can be used to suppress the pain. These drugs work by inhibiting the production of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which are responsible for the activation of the pathways of pain sensation by prostaglandins or thromboxanes. It is believed that the inhibition of COX-2 leads to the anti-inflammatory and analgesic effects, while inhibiting COX-1 may cause gastrointestinal bleeding and ulcers. Therefore, specific COX-2 inhibitors were developed, pairing efficacy in reducing symptoms of RA with reduced gastrointestinal toxicity in comparison with more traditional NSAIDs. [34] Unfortunately all NSAIDs share an unfavorable cardiovascular and renal risk profile. [35] Therefore their use should be restricted to short periods of time and specific clinical situations.

Disease-modifying anti-rheumatic drugs (DMARDs) are the cornerstone in the treatment of RA. [36-38] The term originates from the capability of these drugs to prevent bone erosions. This broad group of DMARDs can roughly be divided into two groups.

Firstly, the synthetic DMARDs are small molecules modulating and suppressing the immune system. This type of DMARDs consists of conventional and recently also more targeted synthetic DMARDs. Currently, the most used conventional DMARDs are Methotrexate (MTX), Sulphasalazine (SSZ),Leflunomide (LEF) and Hydroxychloroquine (HCQ). These 'traditional' drugs all have proven their effectiveness in treating patients with RA, with an acceptable safety profile. The

new class of targeted synthetic DMARDs comprises the Janus Kinase (JAK) inhibitors, which were recently introduced to the pharmaceutical market. This oral compound might have its merits, but the long-term results and the efficacy/safety balance are not yet clear. [39]

Secondly, the biological DMARDs, also called biologics, are biotechnological drugs with a very specific target, located in one of the pathways of inflammation or auto-immunity. [40] These drugs have a tendency to work more rapidly than conventional synthetic DMARDs. Roughly, two groups can be distinguished. A first group of biologics consists of the anti-TNF drugs. As described above, TNF-alpha is a key cytokine in the pathophysiology of RA and by its inhibition inflammation is suppressed. The following biologicals belong to this group: Adalimumab, Certolizumab pegol, Etanercept, Golimumab and Infliximab. More recently biologicals with other mechanisms of action were introduced, including Abatacept, Rituximab and Tocilizumab. Abatacept acts by modulating T-cell function, Rituximab lowers the amount of specific types of B-cells and Tocilizumab inhibits IL-6. All these targets are again determining elements of the inflammation cascade. A substantial drawback of the biologicals is their high cost. Nowadays however, the patents on some of the drugs in this class have expired or are expiring soon. Hence, biosimilars, expressing a highly similar quality and efficacy profile in comparison with the original biologicals, are currently entering the market. This drastic economic change could influence the future affordability and use of biologic therapy in the treatment of RA. [41]

GCs are already commonly used from the fifties in the treatment of RA. Also this class of drugs can be considered as DMARDs, albeit somewhat atypical. GCs bind to the glucocorticoid receptor, which among other things regulates genes controlling the immune system. Thus, GCs rapidly suppress the over-active immune system and as a result, inflammation will be reduced. Besides suppression of inflammation and immune modulation, GCs have a range of other biologic effects in different organ systems, raising concerns because of the potential adverse events related to this. However, decisive evidence on safety is lacking [42, 43].

An important side remark to this list of pharmacological treatment is the speed of treatment response after medication intake. Roughly, two categories exist. The first category consists of the slow acting anti-rheumatic drugs. For example, Methotrexate reaches its maximum potency after three to four months of treatment. Logically, the second group consists of fast acting anti-rheumatic drugs, quickly suppressing pain and inflammation. Biologicals are an example, but the most known members of this family are GCs. In that respect, GCs are useful for bridging the interval between initiation of DMARD therapy and onset of their therapeutic effect. A further discussion point can consist of whether GCs can be regarded as DMARDs or not. Some physicians regard GCs as pure symptomatic treatment, while most studies show that GCs have the ability to prevent bone erosions, the definition of a DMARD. In this discussion, GC dosage and duration should be taken into account. These two factors probably influence its DMARD-like abilities. [43-45]

Treatment strategies for RA

Pharmacological treatment strategies for patients with early RA have changed in recent history. Only two decades ago, physicians would act on a 'go low, go slow' base. Patients were to be treated conservatively and mainly symptomatically. The paradigm was to first initiate treatment with symptom relieving drugs, such as NSAIDs and analgesics, and if insufficiently effective, to add a DMARD like SSZ or MTX. This approach embodied the classical pyramid strategy. As a consequence of this slow approach, the burden of disease for patients with RA was high, not only short-term but also in the long run. Important structural damage and disability were very common in patients with established RA. Many drugs for RA were used with a suboptimal strategy and some older therapeutics are now considered inadequate. At the end of the 20th century, the armamentarium to combat this condition was enlarged and strengthened, not only by a new range of therapeutic agents, with the introduction of the biologicals, but foremost by new therapeutic regimens based on existing drugs. It became clear that intensive and early treatment with optimized medication schedules often combining different anti rheumatic drugs, including traditional DMARDs but also GCs, in a treat to target approach, resulted in much better clinical outcomes than held possible. [46-50] In the current era of increasing therapeutic choices, rheumatologists are challenged to choose the treatment strategy that guarantees the best possible disease outcome for every individual patient, ideally fulfilling both clinicians' and RA patients' treatment goals. Moreover, these goals should be achieved within reasonable cost boundaries. [51] Current international guidelines recommend treating RA patients early, intensively and to target. [36-38] However, these treatment recommendations still leave much room for interpretation by the treating rheumatologist.

The first principle is to treat a patient early. The time elapsed between RA symptom onset and treatment initiation influences treatment outcome, particularly if DMARD monotherapy or a slow step-up strategy is chosen as initial therapeutic approach. [52-54] A better treatment outcome is expected when treatment is initiated earlier than 12 weeks after symptom onset. Hence, treatment delay is of

interest for the rheumatologic community. However, treatment delay is found to be too long in many countries. [55] This total treatment delay is influenced by patient, General Practitioner (GP) and rheumatologist-related factors and strongly dependent on the healthcare system. At these different levels there are opportunities to minimize delay and optimize early RA treatment. There is evidence that the longer it takes to start a treatment, the more important it is to start a combination therapy. [56]

Given the evidence above, the treatment focus is sometimes even shifted to undifferentiated arthritis (UA), which can be partly viewed as a precursor of RA or even a very early stage of RA itself, especially in case ACPA is positive. [57] The rationale is to tackle the disease before RA can fully develop. Treating these patients indeed postpones the evolution to classical RA and inhibits radiographic damage as shown in the PROMPT study. [58, 59] However, treating all patients with UA holds a danger for overtreatment, because the majority of UA patients do not develop RA.

The second principle is to treat intensively with DMARDs as the basis of treatment. [36-38] All international guidelines recommend MTX as gold standard in RA treatment at present, because of its effectiveness and safety profile. [60] The question that many physicians encounter in daily practice is if combinations of slow and fast acting anti-rheumatic drugs are more effective than plain MTX monotherapy in patients with early RA. In the late nineties, the effectiveness of combination therapy with DMARDs versus monotherapy was studied. No benefit of the combination of MTX and SSZ compared to only MTX or SSZ is observed in early RA. [48] Other trials however showed that combination therapy was more effective than monotherapy in refractory RA. [61, 62] At the same time, the potential advantage of adding a low dose of GCs to the anti-rheumatic therapy was studied in more detail, showing that GCs could effectively inhibit radiographic damage. [63] The indications found in these studies were a source of inspiration for one of the hallmarks of early RA trials: the COBRA trial. This study showed that a combination of DMARDs with a remission induction scheme of GCs was superior over DMARD monotherapy. [46] Other concurrent trials demonstrated

similar results. [47, 49] However, SSZ monotherapy was chosen as the comparator in the COBRA study, and it remained unclear if MTX monotherapy was less effective than DMARD combination therapy with GCs as well. In 2007, the BEST trial showed that DMARD combination therapies, supplemented with a remission induction scheme with GCs or a biological, were superior to MTX monotherapy, even in the context of a treat to target strategy. Moreover, combination strategies with a TNF blocker as fast acting compounds showed similar efficacy as a DMARD combination with GC remission induction. [64]

The last but certainly not the least principle is treating a patient to a certain predefined clinical target. This important principle emerged at the beginning of the 21th century. The TICORA and CAMERA trials showed that adapting therapy in case the goal set for disease outcome was not reached, gave superior treatment results. [50, 65] Hence, patients with early RA should be treated to target and as a consequence followed in a tight control setting. This standard indicates that a patient should be monitored regularly to control if the outcome aims are reached and alter the treatment schedule if necessary [36-38]. Treating to target but with too long stretches of time in between clinical evaluations unfortunately nullifies the advantage of rapidly adapting the treatment to an individual patient's needs. The adagio 'you cannot manage what you do not measure' should be honored [6].

Starting from treatment initiation, the primary goal should be clinical remission or at least low disease activity, which is most easily achieved with a 'hit hard, hit fast' approach. In the field of rheumatology, physicians theoretically have the choice between GCs or an array of biological DMARDs in combination with MTX to aim for remission. The BEST trial compared remission induction with GCs and with biological therapy and found comparable efficacy. [64] In practice however the choice is restricted by economic and other constraints incorporated in guidelines and reimbursement criteria. Expensive biological therapy combined with MTX gave superior effects versus MTX monotherapy in several pivotal RCTs mostly without a treat to target approach, and this with remission rates ranging between 20-60%. [66-74] Trials using the cheaper GCs combined with MTX

showed remission rates ranging between 30-70%. [46, 59, 64, 75-78] Yet, most of these trials touched only upon low dose GC use, while increasing attention is given to GCs in moderate or high doses as part of remission induction at treatment initiation. Induction therapies including GCs are often perceived as complicated because of concerns about the broad spectrum of potential adverse reactions. [79] However, evidence for increased numbers of adverse events when using low-dose or high-dose GCs in the short term is scarce [42, 43]. Furthermore, GCs and biological therapy have even been combined for remission induction, with excellent clinical results. [80, 81] In conclusion, remission induction with GCs seems to be a very effective initial therapy choice without economic restraints and with good feasibility in daily clinical practice. [51, 82]

Patients who are refractory to this initial therapeutic approach with synthetic DMARDS and GCs currently have several options with biologicals. To note is that this vast and expensive array of biological DMARDs performs better when combined with a traditional DMARD such as MTX. [40] Economic constraints might influence optimal treatment choices and interfere sometimes with guidelines. Inequities in access to treatment are seen for example in countries with lower socioeconomic welfare. These countries tend to have also stricter eligibility criteria for biologicals. [83]

The window of opportunity

According to the window of opportunity theory, in the first months after diagnosis of RA, intensive treatment should be initiated as soon as possible to achieve remission rapidly, to prevent radiographic progression and to increase the chance of long-term remission. [84, 85] This period in which therapy is more successful seems to be limited by rather stringent boundaries. Recent studies have shown that patients are more responsive to RA treatment only within the first 20 weeks after symptom onset. [86, 87] Furthermore, to benefit maximally from the window of opportunity, following prompt treatment initiation any sign of RA disease activity should be treated and controlled as soon as possible with regular adjustment of treatment in case of insufficient response. [50, 88]

In contrast to the evidence above, the SWEFOT and the recent TEAR trial showed that add-on therapies, starting with MTX monotherapy but rapidly adding synthetic or biological DMARDs after MTX failure yield comparable efficacy rates after one year compared to initial combination therapy. [89, 90] However, the burden of disease for patients over time was not considered in these exercises. Every extra week, or even day, it takes to achieve remission counts in terms of the individual patients' quality of life. From our point of view choosing a treatment strategy that leads to a delay in disease control compared to the optimal therapeutic approach cannot be defended, even if it ultimately results in a comparable disease activity level at a cross-sectional measurement point later on in the disease course, i.e. after one year of treatment. The way a patient reaches an endpoint is at least as important as the endpoint as such, certainly taking into account the patient perspective. Furthermore, the initial response is shown to be probably the driver for good clinical outcomes in the long run. [84, 85]

Nevertheless, some questions remain unanswered regarding the optimal initial therapy for early RA. The COBRA and BEST trial showed that MTX and SSZ combined with a GC remission induction scheme starting at 60mg/day prednisone was superior compared to MTX or SSZ monotherapy. [46, 64] The added effect of SSZ in this regimen and the initial high dose of prednisone are however up for discussion. The Cobra-light study first explored the original COBRA scheme versus an attenuated scheme leaving out SSZ and using less prednisone in the remission induction scheme, starting at 30 mg/day, tapered to 7.5 mg/day in 9 weeks. This trial provided the first clues that an attenuated Cobra scheme could possibly give similar results. [78, 91] However, it was underpowered, administered a different suboptimal dose of MTX at baseline in the comparison group, used a comparable total cumulative prednisone dosage in both groups and had rapid add-on of anti-TNF therapy build in the protocol. The results were thus ambiguous. Other trials such as CARDERA, tREACH and IMPROVED also used some form of an attenuated Cobra scheme with excellent clinical results. [59, 76, 92, 93]

The CareRA trial

Because strong evidence regarding the optimal composition of RA treatment regimens based on the Cobra scheme was still lacking and the feasibility in daily practice was often questioned, the Care in early RA (CareRA) trial was initiated. This trial has served as the backbone of my thesis.

The CareRA study is a two year prospective, multicenter, investigator-initiated, randomized clinical trial. In total, thirteen Flemish rheumatology practices have actively participated: two academic centers, seven general hospitals and four private practices. DMARD naive patients with RA, as defined by the ACR 1987 revised classification criteria were recruited between January 2009 and May 2013. These adult patients were included if their disease duration, the period between RA diagnosis and treatment initiation, was less than or equal to one year. Patients having contra indications for the applied treatments as judged by their rheumatologist were excluded. These patients with early RA were then stratified into a high or low-risk group based on the presence of erosions, RF and/or ACPA; and low or high disease activity. Subsequently, the high-risk patients were randomized to one of three possible intensive treatment strategies with a high or moderate initial dosed GC remission induction scheme. On the other hand, the low-risk patients were randomized in a conservative step up or an intensive step down approach. This rough description of the CareRA trial will be put into more detail further in this thesis.

Aims of the thesis

In summary, treatment prospects for patients with RA have improved greatly compared to the past. However, still many questions regarding the optimal strategy for identification, stratification and treatment initiation in early RA patients remain unanswered. In this PhD project, we aim to optimize the management for every patient with early RA, irrespective of the clinical presentation. Therefore, we put forward three research questions:

1. How long does it currently take before treatment can be initiated in early RA and what are the determinants of a potential delay?

   Chapter 1: Treatment delay in RA care

2. Is a personalized treatment approach feasible with the current prognostic biomarkers?

   Chapter 2: Therapeutic prognostic factors: value and future

3. What is the optimal intensive treatment regimen for early RA?

   Chapter 3: Optimal intensive treatment

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CHAPTER 1

Treatment delay in RA care

Page 28 De Cock D, Meyfroidt S, Joly J, Van der Elst K, Westhovens R, Verschueren P. A detailed analysis of treatment delay from the onset of symptoms in early rheumatoid arthritis patients. Scandinavian journal of rheumatology. 2014;43(1):1-8.

A detailed analysis of treatment delay from the onset of symptoms in patients with early Rheumatoid Arthritis

ABSTRACT

Objectives: A treatment delay above 12 weeks can negatively affect treatment response in Rheumatoid Arthritis (RA). Our aim was to quantify the different stages of delay before RA treatment in different rheumatology centers and to explore influencing factors.

Methods: 156 DMARD naive early RA patients were included from eight practices: one academic hospital, five general hospitals and two private practices. Eight different types of delay were defined from symptom onset till treatment initiation. Information on the duration of each stage of delay was collected from the patient, their general practitioner (GP) and patient files at the rheumatology practice. Patient/GP demographics and disease activity/severity parameters were registered.

Results: The median total delay from symptom onset until treatment initiation was 23 weeks whereas patient-, GP- and rheumatologist-related median delay was 10, 4 and 7 weeks respectively. Only 21.6% of patients had a total delay below 12 weeks. Total median delay in private rheumatology practices was shorter compared to academic and general hospitals ($p<0,001$). Furthermore, RA patients treated within less than 12 weeks showed a higher level of disease activity. The duration of rheumatologist related delay was inversely correlated with disease activity parameters. Patients with morning stiffness were treated sooner, on average 3 weeks, than those without morning stiffness ($p<0,006$).

Conclusion: In only one out of five early RA patients, treatment was initiated within less than 12 weeks as recommended. Patient-related delay contributed most to overall delay. Disease activity and type of rheumatology center seem pivotal determinants of delay.

Introduction

Rheumatoid Arthritis (RA) is a chronic, systemic inflammatory disorder, which can inflict joint destruction and malformation resulting in functional disability (1, 2). A delay in initiating therapy could adversely affect treatment outcomes such as disease activity, remission, functional capacity, and radiographic progression (3-12). It has been demonstrated that the best predictor for a beneficial disease outcome consists of treating RA patients as early as possible. A period of 12 weeks between symptom onset and treatment start is found to be the threshold between favorable or adverse disease outcomes (13, 14). Thus, intensive therapy should be initiated as early as possible (15), with the first three months after RA symptom onset representing a therapeutic window of opportunity (16, 17). Likewise, the European League Against Rheumatism (EULAR) recommendations and the National Institute for Health and Clinical Excellence (NICE) guidelines state that therapy should be initiated as soon as RA diagnosis is made (18, 19). The American College of Rheumatology (ACR) recommendations are somewhat less clear in that respect (20).

Current reports documenting time from symptom onset to treatment initiation in different countries show a delay ranging from a median of 6 to 42 months (21-27). These papers also demonstrate that only a minority of the population is treated in less than 12 weeks ranging from 8% to 42% of patients.

The total treatment delay is determined by patient-, disease- and physician-related factors but also by differences in healthcare organization and referral pathways across various countries (25). Total treatment delay can be divided in two segments.

The first segment is patient related. This delay is the time elapsed between time of onset of RA symptoms and the first appointment with a healthcare professional. In some countries this type of delay contributes the most to the total delay (25, 28). It is influenced by various factors such as RA disease severity and help seeking behavior of the patient (29-32).

The second segment of total treatment delay is physician related. It consists of the time between the first appointment with a health care provider, usually a general practitioner (GP), and initiation of therapy. The physician delay is primarily associated with the effectiveness of the intervention by treating physicians such as the GP or the rheumatologist: rapidity of the diagnostic process, promptness of referral and therapeutic decisiveness. Moreover, various other factors influence referral or time to treatment initiation (29, 33-36). For example, women are referred later than men (37, 38) and DMARDs are initiated earlier in patients without concomitant musculoskeletal conditions (39).

The main aim of this prospective study was to quantify total treatment delay and the different stages of delay across different rheumatology centers and to verify and elaborate the existing knowledge on delay using a different data collection methodology involving patients as well as GP's. Furthermore, we aimed to identify differences between types of rheumatology centers and to investigate potential patient-, GP- and disease- related determinants of delay. A better insight in determining factors might be beneficial for organizing RA care.

Patient and methods

Study Design

This study was performed as a side project of the CareRA study, an ongoing multicenter prospective randomized controlled trial comparing different intensive initial combination treatment strategies in early RA (EudraCTnumber: 2008-007225-39). Diagnosis of RA was defined by the 1987 revised RA criteria. Early RA was defined as a disease duration less than or equal to one year. A total of 262 consecutive DMARD naïve early RA patients were included between February 2009 and January 2012 by 23 rheumatologists in eight Rheumatology Centers across Flanders.

The Ethics committee of the University Hospitals Leuven approved this study and all patients gave their written informed consent.

To the GPs of all 262 patients, a letter was sent requesting the following information about their patients: date of first RA related GP contact, duration of RA related symptoms before seeking help according to the GP and date of referral to a rheumatology center. The following GP demographics were also registered: age, gender and experience with RA. Their level of experience was assessed by asking for the length of their professional career and the number of RA patients, being new patients or subjects in follow-up, they were seeing in their practice per year. GPs were contacted through the treating rheumatologists by regular mail as of February 2012. A reminder was sent after a month to the GPs not responding to the first mailing.
Ultimately, we received the information of 156 patients from 150 GPs corresponding to a GP response rate of 60%. Thus, the data of 156 out of 262 patients could be studied. These patients were seen in eight different rheumatology centers, all participating in the CareRA study. Of these eight centers, one was an academic hospital, five were general hospitals and two were private rheumatology practices.

At their first visit to the rheumatology center and before treatment initiation, patient demographics and disease activity and severity parameters were registered. Continuous variables were age, BMI, DAS28(CRP), visual analogue scales (0-100) such as the Patient Global Assessment (PGA), Physician Global Assessment (PhGA), pain and fatigue, Health Assessment Questionnaire (HAQ; 0-3), Tender Joint Count (TJC), Swollen Joint Count (SJC) and morning stiffness in minutes. Dichotomous variables were gender, smoking and drinking habits, employment status until symptom onset and at treatment initiation, presence of morning stiffness, presence of nocturnal pain, presence of Rheumatoid Factor (RF), presence of Anti-Citrullinated Protein Antibody (ACPA)and erosion status.
Patients were verbally asked by the rheumatologist or the staff for the date of onset of their first RA symptoms. The rheumatologist registered the date of RA diagnosis, date of first visit to the rheumatology center and date of treatment initiation in the patient file.

Outcomes of interest

The collected dates were used to construct eight types of delay:

- Patient delay according to the patient: time elapsed between symptom onset as viewed by the patient and 1st visit to a GP regarding RA symptoms
- Patient delay according to the GP: time elapsed between symptom onset as observed by the GP and 1st visit to a GP regarding RA symptoms
- GP delay: time elapsed between 1st visit to a GP and referral to a rheumatologist
- Rheumatologist delay 1: time elapsed between referral to and 1st screening by rheumatologist
- Rheumatologist delay 2: time elapsed between 1st screening by rheumatologist -start of treatment
- Total rheumatologist delay: time elapsed between referral to rheumatologist-start of treatment
- DMARD initiation delay: time elapsed between diagnosis of RA and start of treatment
- Total delay: time elapsed between symptom onset and start of treatment

Because the information to calculate these different stages of delay came from different sources, in some cases a certain delay was found negative. A negative patient delay could be caused by a patient reporting the date of symptom onset after consulting their GP for their symptoms. Considering that a delay by definition could not be lower than zero, such cases were removed.
Negative values for GP (5) and rheumatologist delay 1 (2) were marginal, but 31 negative values for patient delay were calculated.

Statistical analysis

Data are presented as mean values and standard deviations (SD) or as median values and interquartile range (IQR) depending on the distribution of the data. Comparisons between the same stages of delay across different centers were made with the Wilcoxon or Kruskal–Wallis test. The different levels of delay within the total population were compared using the Wilcoxon signed rank test. Characteristics of patients with early treatment (ETRA: total delay ≤ 12weeks) and patients with late treatment (LTRA: delay > 12 weeks) were compared with the Chi-square or the Wilcoxon test. Spearman's test was used to assess the correlation between different stages of delay and patient/GP demographics or disease activity and severity parameters. A stepwise multiple linear regression

model was constructed to test the influence of different correlating variables on total delay. Delay was log transformed to resolve the skewed distribution.
Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17.0. All statistical tests were two-sided and evaluated at the 0.01 significance level. This level was chosen to correct for multiple comparisons. We choose not to perform a Bonferroni correction because the resulting significance level would be too small to detect any statistically significant difference resulting in false negative outcomes.

Results

Study population

Table 1 displays the patients' characteristics of our study population. This was a typical RA population with a majority being female and ACPA/RF positive.

Data on the referral process of these 156 patients were provided by 150 GP's (65% male) with a mean age (±SD) of 51 (±11) years, with a mean (±SD) experience of 25 (±11) years and seeing a mean number of 13 (±12) RA patients per year.

To control for selection bias we compared the characteristics of our study population of 156 patients with those of all 262 consecutive patients recruited in the CareRA study between February 2009 and January 2012. No significant differences were found (data not shown).

Table 1: Patients' characteristics of the study population

	Study population (n=156)
Age (years)	51 (±13)
Female Gender (%)	68.6%
BMI (kg/m²)	26.4 (±4.4)

Smokers (%)	28.2%
Alcohol Consumption (%)	58.3%
Previously Employed (%)	64.7%
Currently Employed (%)	55.8%
PGA (0-100)	53.3 (±24.3)
Pain (0-100)	53.9 (±24.5)
Fatigue (0-100)	46.4 (±25.0)
PhGA (0-100)	52.1 (±18.6)
Noctural Pain (%)	63.5%
Morning Stiffness (%)	67.1%
Morning Stiffness (minutes)	122.3 (±93.2)
RF present (%)	73.7
ACPA present (%)	71.6
TJC total	13.4 (±8.4)
SJC total	10.4 (±6.8)
TJC 28	8.1 (±5.4)
SJC 28	6.8 (±5.0)
Erosions present (%)	20.5%
DAS28(CRP)	4.70 (±1.16)
HAQ (0-3)	0.98 (±0.64)

BMI= Body mass index; PGA= Patient global assessment; PhGA= Physician global assessment; DAS28(CRP)= 28 joint Disease activity score calculated with C-reactive protein; HAQ= Health assessment questionnaire; TJC= Tender joint count; SJC= Swollen joint count; RF= Rheumatoid factor; ACPA= Anti-citrullinated protein antibody; n= Number of patients. Previously employed was defined as employment at disease onset. Morning Stiffness as a categorical variable was defined as lasting at least 1 hour.
Values given are percentages for discrete variables or mean and standard deviation(SD) for continue variables

Different stages of delay

Table 2 shows the different types of delay for the total population and compares these stages of delay between the three different types of rheumatology centers. Overall, the median total delay was 23 weeks; whereas patient, GP and rheumatologist delay were 10, 4 and 7 weeks respectively. Only 21.6% of the

patients had a total delay ≤ 12 weeks. In academic and general hospitals, patient delay contributed the most to overall delay. In a private practice setting, patient and rheumatologist delay added both equally to total delay. GP delay contributed the least to total delay in all settings.

Table 2: Comparison of each level of delay in early RA patients in the three types of rheumatology settings.

	All settings	Academic Hospital	General Hospital	Private Practice	p-value
Number of patients	156	55	53	48	
Patient delay in weeks (IQR)	10 (4-22)	11 (3-34)	12 (4-26)	5 (2-13)	0,076
Patient delay according to the GP in weeks (IQR)	10 (4-24)	8 (3-22)	14 (8-26)	5 (2-20)	0,061
GP delay in weeks (IQR)	4 (0-13)	4 (1-20)	4 (0-14)	2 (0-10)	0,431
Rheumatologist delay type 1 in weeks (IQR)	6 (3-11)	7 (2-11)	7 (5-12)	5 (3-10)	0,181
Rheumatologist delay type 2 in weeks (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0,861
Total Rheumatologist delay in weeks (IQR)	7 (4-12)	7 (3-14)	8 (5-14)	6 (3-11)	0,077
DMARD initiation delay in weeks (IQR)	1 (0-3)	1 (0-4)	2 (2-4)	0 (1-3)	0,520
Total delay in weeks (IQR)	23 (14-43)	32 (18-51)	25 (15-43)	17 (11-23)	<0,001

GP= General practitioner; IQR= Interquartile ranges.
P-values represent the result of the statistical comparison between delays in academic hospitals, general hospitals and private practices. All tests were conducted at the 0.01 significance level.
Values given are median and interquartile ranges.

Total delay in private rheumatology practices was shorter compared to academic and general hospitals (p<0.001). No statistically significant differences in delay were detected between academic and general hospitals.

Comparisons between the different stages of delay in the total population showed that GP delay was statistically significantly shorter than patient delay (p<0.001), but not shorter than total rheumatologist delay (p=0.024). GP delay and

rheumatologist delay, and patient delay according to the patient and patient delay according to the GP did not differ (p=0.492 and p=0.919).

Early versus late treated RA patients

Table 3 displays the comparison between patients' characteristics of the early treatment group and late treatment group. Patients treated early showed a statistically significantly higher PhGA and pain score at the time of study recruitment compared to patients treated after more than 12 weeks. Patients treated early also tended to have a higher PGA, DAS28(CRP) and HAQ score, to be RF positive and to suffer more from nocturnal pain.

Table 3: Comparison of the characteristics of two categories of patients with different lengths of total delay

	ETRA (n=34)	LTRA (n=122)	p-value
Age (years)	49.4 (±13.8)	50.9 (±12.6)	0.609
Female Gender (%)	70.6%	68.0%	0.776
BMI (kg/m²)	26.6 (±5.1)	26.4 (±4.1)	0.813
Smokers (%)	38.2%	25.4%	0.277
Alcohol Consumption (%)	47.1%	61.5%	0.132
Previously Employed (%)	61.8%	65.6%	0.681

Currently Employed (%)	52.9%	56.6%	0.707
PGA (0-100)	61.1 (±22.3)	51.1 (±24.5)	0.035
Pain (0-100)	64.1 (±21.9)	51.1 (±24.5)	0.007
Fatigue (0-100)	50.9 (±23.3)	45.2 (±25.4)	0.346
PhGA (0-100)	61.4 (±20.6)	49.6 (±17.2)	0.002
Noctural Pain (%)	71.9%	59.8%	0.075
Morning Stiffness (%)	67.6%	63.1%	0.626
Morning Stiffness (minutes)	145.8 (±89.8)	113.5 (±96.0)	0.324
RF present (%)	85.3%	70.5%	0.083
ACPA present (%)	76.5%	70.2%	0.477
TJC total	13.4 (±9.5)	13.4 (±8.1)	0.575
SJC total	11.9 (±8.5)	9.9 (±6.2)	0.404
TJC 28	8.7 (±6.6)	8.0 (±5.0)	0.931
SJC 28	7.1 (±6.5)	6.5 (±4.4)	0.432
Erosions present (%)	17.6%	21.3%	0.640
DAS28(CRP)	5.06 (±1.29)	4.60 (±1.10)	0.060
HAQ (0-3)	1.20 (±0.65)	0.93 (±0.63)	0.031

ETRA= Early treated RA patients= total delay≤12weeks; LTRA= Late treated RA patients= total delay>12 weeks. BMI= Body mass index; RF= Reumatoid factor; ACPA= Anti-citrullinated protein antibody; PGA= Patient global assessment; PhGA= Physician global assessment; DAS28(CRP)= 28 joint Disease activity score calculated with C-reactive protein; HAQ= Health assessment questionnaire; total TJC= Tender joint count 68; total SJC= Swollen joint count 66. n= Number of patients. Alcohol consumption is defined as intake of any amount of alcohol. Morning Stiffness as a categorical variable was defined as lasting at least 1 hour. All tests were conducted at the 0.01 significance level.
Values given are percentages for discrete variables or mean and standard deviation(SD) for continuous variables.

Table 4 shows that patient delay is the main determinant of the difference in total delay between patients with early and late treatment initiation.

Table 4: Relative importance of the different stages of delay for each patient subgroup defined by the total delay before treatment initiation

	ETRA (n=34)	**LTRA (n=122)**	**p-value**
Patient Delay in weeks (IQR)	2 (1-4)	13 (6-27)	<0.001
Patient Delay according to GP in weeks (IQR)	8 (3-31)	12 (4-24)	0.327
GP Delay in weeks (IQR)	1 (0-7)	4 (0-15)	0.142

Rheumatologist delay type 1 in weeks (IQR)	5 (1-8)	7 (3-12)	0.025
Rheumatologist delay type 2 in weeks (IQR)	0 (0-0)	0 (0-1)	0.013
Total rheumatologist delay in weeks (IQR)	5 (2-8)	7 (4-14)	0.012
DMARD initiation delay in weeks (IQR)	1 (0-2)	2 (0-4)	0.003
Total delay in weeks (IQR)	9 (8-11)	29 (21-48)	<0.001

ETRA= Early treated RA patients= total delay≤12weeks; LTRA= Late treated RA patients= total delay>12 weeks. n= Number of patients ; IQR= Interquartile ranges. All tests were conducted at the 0.01 significance level.
Values given are median and interquartile ranges.

Factors influencing the stages of delay

Table 5 shows the correlation between the different stages of delay and patients' characteristics or disease activity and severity parameters. Patient delay was not found to be statistically significantly correlated with any of these parameters. Most rheumatologist related stages of delay were inversely related to disease activity and severity parameters.

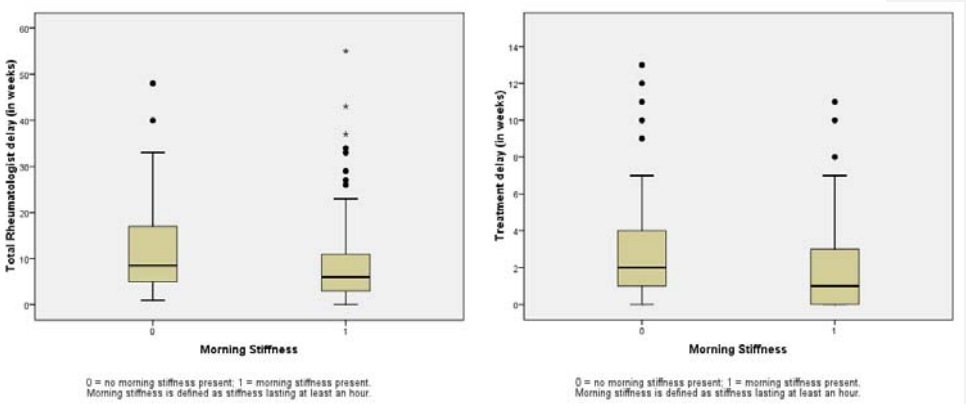
Table 5: Correlations between stages of delay and patients' characteristics measured at the time of recruitment to the study

	GP delay	Rheumatologist delay type 1	Rheumatologist delay type 2	Total Rheumatologist delay	DMARD initiation delay	Total delay
PGA	-0.110	-0.071	-0.129	-0.077	-0.259*	-0.135
Pain	-0.167	-0.059	-0.153	-0.065	-0.285*	-0.183
PhGA	-0.282*	-0.213	-0.144	-0.232*	-0.227*	-0.257*
TJC	-0.105	-0.074	-0.256*	-0.116	-0.246*	-0.028
SJC	-0.100	-0.120	-0.273*	-0.158	-0.261*	-0.165
TJC28	-0.077	-0.174	-0.206	-0.205	-0.303*	-0.078
SJC28	-0.028	-0.136	-0.224*	-0.163	-0.303*	-0.128
DAS28(CRP)	-0.067	-0.236*	-0.273*	-0.273*	-0.387*	-0.179
HAQ	-0.021	0.170	-0.216*	-0.142	-0.300*	-0.161

PGA= Patient global assessment; PhGA= Physician global assessment; DAS28(CRP)= 28 joint Disease activity score calculated with C-reactive protein; HAQ= Health assessment questionnaire; TJC= Tender joint count; SJC= Swollen joint count. Results marked with an asterisk are significant at the 0.01 significance level. Patient delay is not displayed because no variables correlated with this type of delay. Values given are correlation coefficients.

Figure 1 displays statistically significant differences in the length of different stages of delay depending on certain patients' characteristics. Patients with morning stiffness at recruitment to the study had shorter total rheumatologist and DMARD initiation delay compared with subjects without morning stiffness.

Figure 1: Differences in the length of different stages of delay depending on morning stiffness



Morning Stiffness	Yes	No	p-value
Total Rheumatologist delay in weeks (IQR)	6 (3-11)	9 (5-17)	0.006
DMARD initiation delay in weeks (IQR)	1 (0-3)	2 (1-4)	0.002

IQR= Interquartile ranges. Morning Stiffness as a categorical variable was defined as lasting at least 1 hour. Values given are median (IQR) All tests were conducted at the 0.01 significance level.

Table 6 shows the results of the stepwise multiple linear regression analysis for total delay. All parameters (type of hospital, Pain, PGA, PhGA, TJC, SJC, HAQ and Morning Stiffness) that were correlated with any stage of delay were included at start of analysis, except DAS28(CRP), TJC28 and SJC28. These variables were connected to other variables used in the model and could result in a false

model. SJC and type of hospital were related with total delay. These variables explained together 15% of the variability in total delay. Type of hospital explained 8.4% while SJC explained 6.6%.

Table 6: Stepwise multiple regression models for total delay (in weeks)

Variable	β – standardized coefficient	B (95% CI) - unstandardized coefficient	p-value
Constant		55.980	
Types of hospital	-1.384	-1.339 (-1.531; -1.169)	<0.001
SJC	-1.278	-1.026 (-1.042; -1.010)	0.002

CI= confidence intervals; SJC= Swollen joint count. DAS28(CRP) was not selected as a predictor because it is calculated with the aid of variables (PGA, SJC and TJC) used in the model. SJC 28 and TCJ28 were also not used because these variables are related to the total SJC and TJC. All tests were conducted at the 0.01 significance level. Values presented are geometric means.

Discussion

In this study, the length of different types of delay before treatment initiation was computed. Only approximately one in five of new early RA patients in our large population were treated in less than or equal to 12 weeks, which is the critical period to have most beneficial effects on disease outcome (14). Furthermore, we have shown that differences in delay existed between different types of

rheumatology centers: in private practices, total delay was less pronounced than in academic or general hospitals. Jamal et al already found indications for this trend in their data (40).

A linear regression model showed that the type of practice was the only statistically significant independent determinant of total delay, besides the total swollen joint count. SJC at recruitment to the study was already previously found to have an influence on delay (41). Age and gender were not found to have an influence on total delay in contrast to earlier studies (29, 37). However, despite being built with a large number of variables associated with delay, our regression model could only explain a very small fraction of the variability of total delay. To explore additional determinants of delay, a need certainly exists for further research, including qualitative approaches.

Patient related delay

In the total population, patient delay contributed most to overall delay. This type of delay can be theoretically further subdivided in two parts: firstly, the time between initial onset of symptoms and seeking medical advice and secondly, the time to get an appointment with a GP. This second component of patient delay was probably proportionally less important in our study, due to the way GP appointments are organized in Flanders. Most likely, patient delay was mainly determined by how quick the individual became aware of the nature and the seriousness of the problems (30). This hypothesis was substantiated in our study by two findings. Firstly, patients treated early displayed a relatively shorter patient delay compared with patients treated later than 12 weeks.

Secondly, patients treated early reported more pain and showed a higher level of RA disease activity according to their rheumatologist at treatment initiation.

Patients were asked for the date of symptom onset at treatment start. Memory bias could thus have influenced patient delay as illustrated by the many negative calculations of patient delay leading to exclusion of these patients for further analysis. As a fail-safe, GPs were also requested to check their file when their patients had mentioned possible rheumatic symptoms for the first time. Patient delay according to patient or GP showed similar results in the total population.

GP related delay

GP delay in our study was the least important contributor to the total delay, in contrast to other studies where GP delay contributed the most to overall delay (13, 42). This finding could mean that RA symptoms were rapidly recognized by the GP and the patient was immediately referred to the rheumatologist. Furthermore, the four weeks GP delay found in our study is comparable to GP delays registered in Stockholm and Birmingham, although shorter compared to other centers in the same study (25).

Rheumatologist related delay

The second most important contributor to overall delay was the rheumatologist delay. This type of delay was split into two subtypes: rheumatologist delay type 1 and type 2.

Clearly, rheumatologist delay type 1 contributed the most to total rheumatologist delay. This finding could have two reasons: either the patients waited to make an appointment with the rheumatologist after referral by their GP and/or they struggled to get an appointment. Arguments can be found for the latter. Rheumatologist type 1 delay is shorter in private practices compared with general hospitals and, in absolute numbers, academic hospitals. The logistic pathway in hospitals is probably longer than in more flexible private practices. For example, due to staff hours and limited availability of consultation rooms, appointments in a hospital are more difficult to schedule. Furthermore, rheumatologists in hospitals can have more additional tasks than only the ambulatory care for their patients. Getting the right patient to the right department can also be problematic in large hospitals. Additionally, higher numbers of secondary referrals and a greater complexity of patients could lead to more difficulties and increased delay in academic centers.

Rheumatologist delay type 2 and DMARD initiation delay were both very short, meaning that once patients were screened or diagnosed, they were promptly treated, as was shown in earlier studies (40). All types of rheumatologist delay

are inversely correlated with various disease activity and severity parameters. Presence of morning stiffness at treatment initiation was apparently an important predictor for shorter rheumatologist-related delays. Possibly, patients who have a more active disease, will try to get an appointment more rapidly and rheumatologists will probably be more inclined to treat them faster.

Strengths and limitations

This study has both strengths and limitations. We were able to study a representative sample of the early RA patients participating in the CareRA study. In principle, all consecutive patients diagnosed with early RA between February 2009 and January 2012 were included in this large multicenter RCT, with the participation of almost one third of the Flemish rheumatologists from all provinces. Therefore we consider our results to be a reflection of the current situation in our region, but further data are needed in other health care systems. Another important strength of this delay study is that memory bias was limited as much as possible: analyzing GP log books and hospitals databases minimized this error. To our knowledge, we are the first to use information from the GP concerning the important time points from symptom onset to referral, in order to lower risk of memory bias. The only date that remained difficult to reconstruct with accuracy was the date of symptom onset. The 31 negative values calculated for patient delay as discussed in the methods section underscore this difficulty. This bias was countered by asking the GP when their patient reported RA symptoms for the first time. In writing specifically and only to the GP to inquire for dates of first appointment and referral, we included another possible confounding factor. In Flanders, GPs function as gatekeepers to specialists, so the most logical care pathway to be followed is that the patient first sees the GP and afterwards the rheumatologist. However, patients could also use alternative ways via other specialists to get an appointment with a rheumatologist. This study did not take these potential heterogenic pathways into account. It could be that these routes are a cause of a more prolonged delay. Another limitation of this study is that disease activity parameters could only be measured at recruitment to the study and not at onset of symptoms or any earlier stage. Data from earlier in the disease course could possibly give a more complete picture of the help seeking behavior

of patients or the referral behavior of GPs. Unfortunately this is not achievable without the help of experienced GPs trained in the evaluation of disease activity in early RA.We did no Bonferonni correction for repeated testing in this study which could lead to false positive findings. However, a significance level of 0,01 was chosen to correct for multiple testing while trying to lower the chance of false negatives at the same time.

Conclusion

In conclusion, delay from symptom onset to treatment initiation is still too long with a median of 23 weeks, similar to previous studies (25). Only one out of five patients are seen on time. Patient delay contributes the most to this overall delay. The type of rheumatology center and certain disease activity parameters influence treatment delay and its components. Interventions are needed to lower this delay. Increasing people's awareness of RA, education and development of screening tools (43) for GPs and for other healthcare professionals who are potentially the first to be consulted by early RA patients to make assessments more efficient and to shorten the logistical pathways in rheumatology centers are future opportunities. Early Arthritis Recognition Clinics are an excellent example of such a measure to decrease delay (44).

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CHAPTER 2

Therapeutic prognostic factors: value and future

Page 51 De Cock D, Vanderschueren G, Meyfroidt S, Joly J, Van der Elst K, Westhovens R, Verschueren, P. The performance of matrices in daily clinical practice to predict rapid radiologic progression in patients with early RA. Seminars in arthritis and rheumatism. 2013;43(5):627-631.

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The performance of matrices in daily clinical practice to predict rapid radiologic progression in patients with early RA

ABSTRACT

Objectives: To compare in daily clinical practice the reliability of matrices which forecast rapid radiologic progression (RRP) at year one, at year two and over two years in patients with early Rheumatoid Arthritis (RA).

Methods: 74 early RA patients with X-rays of hands and feet at baseline, year one and year two were included. Initial DMARD combination therapy with steroids (ICTS) or DMARD monotherapy (IMT) was initiated according to patients' RA severity, based on rheumatologist opinion. The images were scored via the modified Sharp/van der Heijde (SvH) method. A total Sharp score progression of equal or higher than five per year was considered RRP. Six matrices were tested: ASPIRE CRP/ESR matrices, the BEST matrix, two SWEFOT matrices and the ESPOIR matrix. Patients were placed in each of them yielding a RRP probability. The performance was tested by Area Under the Curve analysis reflecting the predictive value.

Results: Four patients developed RRP in year one, five in year two and four over two years. With regards to face validity, the predicted probability did not correspond to the risk in reality: the one ICTS patient who developed RRP over two years was always found in the lowest RRP categories of all matrices. The ASPIRE CRP matrix yielded at least a moderate predicting value for the three time points. The other matrices showed moderate to no predicting value.

Conclusion: The performance of all matrices was disappointing and it is impossible to fully rely on the existing matrices in daily clinical practice.

INTRODUCTION

One of the most important targets in the management of Rheumatoid Arthritis (RA) is preventing structural damage and disability in the long term. Many treatment possibilities exist to avert such excessive radiologic progression (1-5). However, a physician must decide for each individual patient separately which treatment is optimal. Rapid radiologic progression (RRP) occurs only in a minority of patients with early RA and it is of key importance to detect these patients.

In the last decade many predicting factors for radiographic progression and RRP were identified, but individually these predictors have only a limited prognostic value (1, 6-19). Therefore, composite predicting models, arranged in so called matrices, were constructed to help the treating physician to detect patients at risk for RRP. Six prediction matrices were identified: the ASPIRE CRP/ESR (20), the BEST (21), the SWEFOT which has two submodels (22, 23) and the ESPOIR (24) matrix. The ESPOIR matrix was the only model developed in an observational cohort while the others originated from clinical trials. Durnez et al. tested the predictive value of the ASPIRE matrix in a daily practice early RA cohort and found that it yielded a strong negative predictive value, but lacked a positive predictive value (25). Furthermore, the ASPIRE, the BEST and the SWEFOT matrix were tested in a cohort of established RA patient and were found to have a limited ability to predict RRP (26). Fautrel et al tested the performance of these matrices on the French ESPOIR cohort and concluded that the BEST matrix had the greatest validity to detect RRP in their population (27).

Our aim was to compare the performance of the existing matrices to reliably predict RRP in an early RA cohort in daily practice in the first year, in the second year and over a period of two years.

METHODS

The patient population for this trial was part of an observational cohort at the department of Rheumatology of the University Hospitals of Leuven. This cohort consisted of consecutive DMARD naïve early RA patients, enrolled between 2001 and 2007 (28). Only patients enrolled in parallel randomized clinical trials (RCT) were excluded. 74 patients were selected for this study because they had X-rays of hands and feet at baseline, year one and year two. Patients received initial combination therapy with steroids (ICTS) or DMARD monotherapy (IMT) and were evaluated at least every four months. 42 Patients received IMT while 32 started ICTS . The disease course of this population was previously published in part (25, 28-30). This study was approved by the Ethics Committee of the University Hospitals Leuven and all patients gave written informed consent before inclusion.

Demographics were registered at baseline and the following clinical characteristics were obtained at baseline, year one and year two: swollen/tender joint counts (TJC , SJC, TJC28 and SJC28), assessment scores by Visual Analogue Scales (VAS patient global-PGA, VAS physician global-PhGA, VAS pain and VAS fatigue), Health assessment questionnaire (HAQ), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Disease activity score based on CRP status (DAS 28(CRP)) was calculated from these parameters.

The X-ray images were scored according to the modified Sharp/van der Heijde (SvH) method (31) by three readers separately: two experienced radiologists (LL and GVDS) and one clinical researcher (DDC). A joint score was only selected when two out of three readers gave this joint a score higher than zero. If joint scores were not equal, the lowest score was selected. The highest score was only selected if two readers scored the joint equally higher than the other reader. This modified method of calculating a general SvH score was used instead of the more common mean scores of all readers or consensus score to minimize potential bias and overestimation of radiographic damage.

A total Sharp score (TSS) progression of equal or higher than five per year was considered RRP. This definition meant that a TSS progression equal or higher than ten between baseline and year two was considered RRP. The threshold of five points matches the destruction of one small joint and the typically reported smallest detectable difference (32, 33).

Six matrices were used in this study: the ASPIRE, the BEST, the SWEFOT and the ESPOIR matrices (table 1). The ASPIRE matrix itself has two sub models: ASPIRE CRP and ASPIRE ESR. The ASPIRE matrices use SJC28, RF status (U/mL) and CRP (mg/dL) or ESR status (mm/h). The BEST matrix consists of baseline erosion scores, RF and ACPA presence combined and CRP status (mg/L). The SWEFOT matrix has two submodels. The first model (SWEFOT1) consists of gender, RF presence, ACPA presence and ESR status (mm/h). This matrix was not developed for detecting RRP, but for detecting any radiologic progression. However, it was deemed interesting enough to be tested in our study. The second model (SWEFOT2) predicts rapid radiologic progression and uses smoking status, presence of erosions and CRP status (mg/L). The ESPOIR matrix uses presence of erosions, ACPA positivity, CRP status (mg/L) and SJC28 as predicting variables. The ASPIRE and BEST matrices yield a different risk probability for patients on mono- or combination therapies.

Table 1: Parameters used in the six tested matrices to predict RRP

Matrix type	SJC28	RF (U/L)	RF +/-	ACPA +/-	CRP status (mg/L)	ESR status (mm/h)	Erosions	Gender	Smoking
ASPIRE CRP	X	X			X				
ASPIRE ESR	X	X				X			
BEST			X	X	X		X*		
SWEFOT1			X	X		X		X	
SWEFOT2					X		X**		X
ESPOIR	X			X	X		X**		

RRP= Rapid radiographic progression; SJC= Swollen joint count RF= Rheumatoid factor; ACPA= Anti-citrullinated protein antibody; CRP= C-reactive protein; ESR= Erythrocyte sedimentation rate. * according to the Sharp/van der Heijde method ** typical RA erosions evaluated by the rheumatologist

One other algorithm was developed from data from an early RA cohort, SONORA, in Canada and the United States (34). However, this matrix uses ACPA titers(U/L). In our observational cohort, this parameter was not available for most of our patients and thus this algorithm could not be tested in this study.

Patients were systematically placed in each of the matrices yielding a RRP probability. The mean RRP probability associated with the expert's initial treatment choice was compared between patients with and without RRP. The performance of the matrices to identify RRP patients was tested by Receiver Operating Characteristic (ROC) curve analysis in which the Area Under the Curve (AUC) reflected the discriminating power. A ROC curve plots the fraction of true positives out of the positives (true positive rate) against the fraction of false positives out of the negatives (false positive rate). In this performance test, we used the probabilities given in the six matrices. A matrix with an AUC of less than 0.5 was considered as having no predicting value, a matrix with an AUC between 0.5 and 0.7 was considered to have moderate predicting value and a matrix with an AUC higher than 0.7 was regarded as having good predicting value.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17.0.

RESULTS

Table 2 shows the descriptive statistics at baseline of the total population and of the rapid progressors in the first year, in the second year and over two years. Four patients developed RRP in the first year. Five other patients developed RRP in the second year. Four patients in total had a TSS progression of more than ten points over two years. Remarkably, three patients out of these four were common between groups with RRP in the first year and the one with RRP over the two-year study period. RRP patients were different in the first and second year.

Table 2: Baseline descriptive statistics of the total population and RRP patients

	Total population	RRP first year	RRP second year	RRP over two years
Number of patients	74	4	5	4
Age (years)	52 ± 16	51 ± 14	43 ± 33	46 ± 18
Gender (female %)	65%	25%	100%	50%
Smoker (%)*	28%	25%	33%	0%
Symptom duration (months)	8 ± 7	8 ± 4	14 ± 13	9 ± 3
Disease duration (months)	1 ± 1	1 ± 2	1 ± 0	1 ± 2
RF positive (%)	71%	75%	60%	50%
RF (U/mL)	224.7 ± 281.1	350.5 ± 296.1	139.6 ± 68.4	200.5 ± 146.6
ACPA positive (%)	71%	50%	80%	50%
ESR (mm/h)	36.66 ± 24.06	44.50 ± 34.91	26.40 ± 13.98	38.75 ± 37.48
CRP (mg/L)	28.80 ±33.78	35.50 ± 46.71	38.40 ± 34.28	51.43 ± 48.92
PGA (0-100)	53.56 ± 24.87	56.00 ± 23.58	67.20 ± 20.19	46.00 ± 8.72
Pain (0-100)	51.52 ±24.39	47.00 ± 39.05	71.40 ± 16.03	38.67 ± 24.66
Fatigue (0-100)	41.70 ±25.42	14.67 ± 12.42	64.20 ± 17.11	40.33 ± 40.22
PhGA (0-100)	42.14 ± 19.36	35.25 ± 7.14	45.33 ± 19.50	33.00 ± 8.52
Total TJC	14.35 ± 10.59	8.25 ± 2.99	14.60 ± 10.02	7.75 ± 2.99
Total SJC	12.45 ± 8.19	7.75 ± 5.50	16.00 ± 10.51	8.75 ± 4.65
TJC28	8.28 ± 6.38	4.25 ± 2.75	7.80 ± 7.46	3.75 ± 3.20
SJC28	8.01 ± 5.35	6.75 ± 5.56	10.00 ± 8.19	6.75 ± 5.56
HAQ score (0-3)	1.10 ± 0.76	1.50 ± 0.78	1.66 ± 1.12	1.79 ± 1.04
DAS28 (CRP) score	4.91 ± 1.22	4.48 ± 0.95	5.21 ± 1.34	4.40 ± 0.98

RRP= Rapid radiographic progression; RRP first year = Rapid radiographic progression between baseline and the first year, defined as a total Sharp score ≥ 5; RRP second year = Rapid radiographic progression between the first and the second year, defined as a total Sharp score ≥ 5; RRP over two years = Rapid radiographic progression between baseline and the second year, defined as a total Sharp score ≥ 10; RF= Rheumatoid factor; ACPA= Anti-citrullinated protein antibody; ESR= Erythrocyte sedimentation rate; CRP= C-reactive protein; PGA= Patient global assessment; PhGA= Physician global assessment; TJC= Tender joint count; SJC= Swollen joint count; HAQ= Health assessment questionnaire; DAS28(CRP)= 28 joint Disease activity score calculated with C-reactive protein. Values given are percentages or mean ± SD.*This is calculated on 65 patients. Data about smoking behavior of nine patients is missing.

For only one patient ACPA status was missing at baseline and data from this patient could not be used in matrices using ACPA status as a variable (BEST, SWEFOT1 and ESPOIR matrices). For nine patients data about smoking status were missing. Likewise, these patients were excluded in the evaluation of the SWEFOT2 matrix.

Table 3 shows radiographic progression in the total population and the groups with RRP between baseline and year one, between year one and year two and between baseline and year one.

Table 3: Radiographic evolution of the population and RRP patients over two years

		Total population	RRP - first year	RRP - second year	RRP over two years
Number of patients		**74**	**4**	**5**	**4**
Baseline	**Radiographic damage**	46%	75%	80%	75%
	TSS	2.62 (±4.94)	2.50 (±5.00)	1.20 (±2.68)	2.50(±5.00)
Year 1	**Radiographic damage**	58%	100%	80%	75%
	TSS	3.69 (±5.78)	13.25 (±5.32)	1.40 (±3.13)	11.00(±8.60)
	Change in TSS	1.07 (±2.59)	10.75 (±2.87)	0.20 (±0.45)	8.50 (±6.25)
Year 2	**Radiographic damage**	66%	100%	100%	100%
	TSS	4.66 (±6.30)	13.75 (±4.86)	9.60 (±5.18)	15.75(±3.76)
	Change in TSS	2.04 (±3.43)	11.25 (±2.63)	8.40 (±4.88)	13.25 (±3.30)

RRP= Rapid radiographic progression; RRP first year = Rapid radiographic progression between baseline and the first year, defined as a total Sharp score ≥ 5; RRP second year = Rapid radiographic progression between the first and the second year, defined as a total Sharp score ≥ 5; RRP over two years = Rapid radiographic progression between baseline and the second year, defined as a total Sharp score ≥ 10; TSS= Total sharp score; Change in TSS is calculated from baseline. Radiographic damage is a TSS larger than 0. Values given are percentages or mean (± SD).

Patients with RRP were systematically placed in each of the matrices yielding a RRP probability. For illustrative purposes, the prediction matrices with RRP patients over two years can be viewed in the supplementary files. With regards to face validity, all matrices gave a confusing image in predicting RRP. The ICTS patient developing RRP over two years was always found in the lowest risk categories except in the SWEFOT2 matrix. Here, the patient was found in the third lowest risk category. The three IMT patients with RRP over two years were found scattered in all risk categories. Only the ASPIRE CRP and ESR matrices put one patient in the highest risk category. Prediction matrices for RRP patients at year one or at year two yielded similar findings.

The predictive capacity of the matrices was measured by calculating the AUC with the aid of ROC curves. Data of patients developing RRP in the first year, in the second year and over two years was used. In the first year, the BEST and the ASPIRE ESR/CRP matrix yielded an AUC between 0.5 and 0.7, which gives them moderate predicting value. The SWEFOT matrices lacked any predicting value with an AUC below 0.5. In the second year, the ASPIRE CRP and SWEFOT matrices displayed an AUC between 0.5 and 0.7, which gives them moderate predicting value. The BEST and ASPIRE CRP yielded an AUC equal or lower than 0.5, which means they have no predictive value at all. Over two years, the ASPIRE CRP matrix displayed an AUC higher than 0,7, which gives it good predicting value. The BEST and ASPIRE ESR matrix yielded an AUC between 0.5 and 0.7, which gives them moderate predicting value. The SWEFOT matrix lacks any predicting value. Table 4 gives an overview of the AUCs of all matrices tested.

Table 4: Matrices with their respective AUC

	Area under the curve to predict RRP		
	First year	**Second year**	**Over two years**
ASPIRE CRP	0.675	0.646	0.704
ASPIRE ESR	0.675	0.368	0.566
BEST	0.599	0.500	0.599
SWEFOT1	0.344	0.535	0.254
SWEFOT2	0.517	0.435	0.407
ESPOIR	0.351	0.502	0.351

RRP= Rapid radiographic progression

DISCUSSION

In this study, the performance of six matrices to predict RRP in daily clinical practice was analyzed at three time points. The ASPIRE CRP matrix showed the highest discriminating power to predict RRP in our observational cohort of early RA patients. This is in contrast to findings in the ESPOIR cohort in which the BEST matrix yielded the best predictive value (27).The overall performance of all matrices was however disappointing in patients with early RA as already demonstrated in patients with established RA by Lillegraven et al (26). First of all, the face validity of the matrices was inadequate and yielded a confusing image of RRP probabilities for all patients when placed in the matrices. Worrisome, the one ICTS patient developing RRP, who was viewed as a high risk patient by his treating physician and thus given an intensive therapy, was always found in the lowest risk categories of all matrices. The ROC analyses revealed that only moderate predicting capacity could be reached by some matrices at some time points. The ASPIRE CRP matrix was chosen to be the most promising matrix because of consistently having moderate predicting value in our population. All matrices use parameters that are commonly used in clinical practice and many use similar variables. However, different cut-offs are used for the same parameters. The poor results seem to show that the matrices are too much tailored on the patient population in which they were conceived and are not applicable in clinical practice, a setting in which they were originally intended to be used. In daily practice, more diverse patients are treated and more dynamic therapeutic strategies are used, which could alter the risk level for radiographic progression in comparison to strictly protocol driven trials. This is a problem for most matrices because they are based on RCT data. The ESPOIR matrix, however, was developed in a large observational cohort of so called “possible RA” patients. Patients treated with methotrexate or leflunomide and with a profile likely to be RA were chosen for the construction of this matrix (24). The selection of patients could partially explain the poor performance of this matrix in our study. In our trial population, no such treatment selection took place: both patients on DMARD monotherapy in a step up approach and patients on combination therapy following a step down approach were included.

The rheumatologists based their therapy choice on an informal evaluation of risk factors. These factors were primarily the presence of erosions at baseline, RF/ACPA status and DAS28(CRP) score. These variables resemble those from the BEST matrix. However, the BEST matrix still lacked predicting power in clinical practice while the treating physicians proved to make a good choice in therapy intensity depending on the risk profile of their RA patients.

The low number of patients in our study could be seen as a limitation. However, the clinical characteristics of our study population are similar to those of the total patient population of our observational cohort, with a less severe profile as compared to our population of patients included in RCT's and compared to the ASPIRE population (25, 28-30). Furthermore, the use of biologics, known to be particularly effective at halting radiographic progression, could in theory have influenced the matrices performance, but only very few patients used these agents in our cohort (30). The ICTS group of our population had a more severe RA profile and was thus more prone to receive biologicals. This could possibly bias our results to a certain extent.

A second limitation could be the low number of patients with RRP in this study. RRP was only present in 5% of patients in the first year, 8% in the second year and 5% over two years. These numbers are low compared to other studies (20). This could be due to chance, given the small sample size. Secondly, our population had a less severe RA profile as stated above. The occurrence of RRP could therefore be reduced. Another reason could be that therapy was chosen by expert opinion. The risk for radiologic progression was apparently estimated quite well and a suitable therapy was chosen. The last and probably most important reason for the low number of patients with RRP in our study is that the tight control principle in this cohort gave the treating physician flexibility to adjust therapy if needed, in contrast to a RCT setting. As proof of success of this principle, RRP patients in the first year had little radiographic progression in the second year. Thus, the few patients with RRP can more be seen as a success of the initial treatment choices and the application of the tight control principle.

In conclusion the low number of RRP cases in this study and the small sample size are no justification for the meager performance of the evaluated matrices. A reliable predicting matrix still should be able to identify the scarce patients at risk in a real life situation to be of help for physicians having to make the difficult initial treatment choice for each individual patient with early RA.

The different time frames defined in this study should be regarded with caution because they partly overlap and the results cannot be interpreted completely independently. However, the value of the three chosen timeframes can be found in the fact that patient characteristics differ in these three periods. Remarkable in our study population are for example the patients developing RRP in the second year. These patients were all female, with a mean age clearly lower than the rest of our population, with a long symptom duration at baseline and a majority being ACPA positive. It could be that in certain subgroups of RA patients, RA severity is underestimated which could affect the treatment choice and consequently the risk on RRP.

CONCLUSION

The predicting performance of the six matrices (ASPIRE CRP/ESR, BEST, SWEFOT 1/2 and ESPOIR matrices) to detect risk of RRP was modest at best. The ambiguity in results points to the need to improve the existing matrices or even to build new predicting matrices for use in daily clinical practice. A collaboration to unite several early RA cohorts with various patient profiles would be beneficial to create a prediction matrix in which rheumatologists could trust.

Supplementary files: Patients with RRP over 2 years systematically placed in each of the matrices yielding a RRP probability.

ASPIRE (ESR) MATRIX – IMT – n=42						
28 SJC	>17	1			>50	ESR (mm/h)
	10-17	2/1		1		
	<10	1	2	3		
	>17				21-50	
	10-17	5	1	2		
	<10	4	3	4/1		
	>17	1			<21	
	10-17	1				
	<10	5	3/1	3		
		<80	80-200	>200		
		RF titer (U/mg)				

blue: 0–9%: green: 10–19%: yellow: 20–29%: orange: 30–39%: red: 40–100%

ASPIRE (ESR) Matrix – ICTS – n=32						
28 SJC	>17				>50	ESR (mm/h)
	10-17			3		
	<10		2	2		
	>17	1		2	21-50	
	10-17	4		2		
	<10	2	3	1		
	>17				<21	
	10-17	1	1	1/1		
	<10	4	1	2		
		<80	80-200	>200		
		RF titer (U/mg)				

blue: 0–9%: green: 10–19%: yellow: 20–29%: orange: 30–39%: red: 40–100%

ASPIRE (CRP) MATRIX – IMT – n=42						
28 SJC	>17	1			>3	CRP (mg/dl)
	10-17	4/1		1		
	<10	2	3/1	3		
	>17	1			0.6-3	
	10-17	2	1	2		
	<10	3	3	3/1		
	>17				<0.6	
	10-17	2				
	<10	5	2	4		
		<80	80-200	>200		
		RF titer (U/mg)				

blue: 0–9%: green: 10–19%: yellow: 20–29%: orange: 30–39%: red: 40–100%

ASPIRE (CRP) Matrix – ICTS – n=32						
28 SJC	>17			2	>3	CRP (mg/dl)
	10-17	1		4		
	<10		2	2		
	>17	1			0.6-3	
	10-17	3		1		
	<10	6	2	1		
	>17				<0.6	
	10-17	1	1	1/1		
	<10		2	2		
		<80	80-200	>200		
		RF titer (U/mg)				

blue: 0–9%: green: 10–19%: yellow: 20–29%: orange: 30–39%: red: 40–100%

BEST Matrix – IMT – n=41						
CRP (mg/l)	≥35	1/1	2		≥4	Erosion score at baseline
			1	1	1-4	
		2	1/1	3	0	
	10-35	1	1	3	≥4	
		1		2	1-4	
		2	1	6/1	0	
	<10		1		≥4	
				2	1-4	
		2	1	7	0	
		-/-	-/+ or +/-	+/+		
		RF and ACPA				

blue: 0–9%: green: 10–19%: yellow: 20–29%: orange: 30–39%: red: 40–100%

BEST Matrix – ICTS – n=32						
CRP (mg/l)	≥35		1		≥4	Erosion score at baseline
			1	4	1-4	
				4	0	
	10-35		2		≥4	
			1	2	1-4	
			1	3	0	
	<10	1		3	≥4	
			2	1	1-4	
		1	4/1	1	0	
		-/-	-/+ or +/-	+/+		
		RF and ACPA				

blue: 0–9%: green: 10–19%: yellow: 20–29%: orange: 30–39%: red: 40–100%

ESPOIR Matrix – n=73							
		Absence of erosions			Presence of erosions		
		SJC<14	14≤SJC<20	SJC≥20	SJC<14	14≤SJC<20	SJC≥20
ACPA +	CRP≥35	5/1**	1	1	5	1	
	4≤ CRP<35	13/1**	2	1	15		
	CRP<4	6			1	1	
ACPA -	CRP≥35	1	1		3/1**	1	
	4≤ CRP<35	5			5	1	
	CRP<4	3/1*			1		

red >50%: orange 25-50%: yellow 10-25%: green <10%

***ICTS patient**

****IMT patient**

SWEFOT1 Matrix – n=73					
RF +	ESR high	1	4	10/1**	17
	ESR low	1	4/1*	6	9
RF -	ESR high	5/1 **	5	3	5
	ESR low		1		2/1**
		Male	Female	Male	Female
		ACPA -		ACPA +	

red 90%: orange 80%: yellow 50%: green 20%: blue 10%

***ICTS patient**

****IMT patient**

SWEFOT2 Matrix – n=65				
		CRP<10	10≤CRP<35	CRP≥35
Smokers	Erosive	1	2	2
	Non Erosive	1	3	3
Non-smokers	Erosive	9	11	9/1**
	Non Erosive	15/1*	11/1**	7/1**

Red 40% Orange 30% Yellow 20% Green 10% White no risk factor given.

***ICTS patient**

****IMT patient**

n= total number of patients used in matrix.

RF= Rheumatoid factor; ACPA= Anti-citrullinated protein antibody; ESR= Erythrocyte sedimentation rate; CRP= C-reactive protein; SJC= Swollen joint count; ICTS= initial combination therapy with steroids; IMT= DMARD monotherapy

Numbers in cells of matrix represent the number of patients with a set of clinical characteristics yielding the RRP probability corresponding to a particular cell in the matrix. Numbers behind a dash show how many of these patients actually developed rapid radiologic progression (RRP). For example, 'X/Y' means that X patients had a particular set of clinical characteristics corresponding to this cell in the matrix and Y of these X patients developed RRP.

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Two year clinical and radiologic follow-up of early RA patients treated with initial step up monotherapy or initial step down therapy with glucocorticoids, followed by a tight control approach: lessons from a cohort study in daily practice.

ABSTRACT

Objectives: To evaluate the effect of initial DMARD combination therapy with steroids (ICTS) and DMARD monotherapy (IMT) on the clinical and radiologic evolution of patients with early RA over a two year treatment period, applying tight control (TC) in daily practice.

Methods: 74 DMARD-naïve early RA patients received ICTS or IMT in a TC setting. Baseline, year one and year two X-rays of hands and feet were scored according to Sharp/van der Heijde. Rapid radiographic progression (RRP) was defined as total Sharp score (TSS) of >5 units/year.

Results: At year one, both treatment groups achieved 50% remission. At year two, 37% of IMT and 60% of ICTS patients were in remission, despite ICTS patients having initially a more severe RA profile.

RRP was found in 4/74 patients at year one: 3 IMT and 1 ICTS patient. Remarkably, 3 of these 4 patients had no radiographic progression in the second year. Five other patients had RRP in the second year: four IMT and one ICTS patient.

Conclusion: In a TC setting, ICTS and IMT can prevent radiographic progression in the majority of patients in the daily practice of a Belgian academic hospital over two years. ICTS seems to be more effective than IMT in achieving higher remission rates and less radiographic progression.

Introduction

Combination therapy with disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (GCs) or biological agents is superior in achieving a clinical response and preventing joint damage compared to DMARD monotherapy in patients with early rheumatoid arthritis (RA). [1-4] Previously it was demonstrated that initial DMARD combination therapy with steroids (ICTS), is feasible in a tight control (TC) setting in daily practice. Additionally, ICTS proved clinically more effective in treating early RA compared with initial DMARD monotherapy (IMT) in daily practice. [5] Furthermore, patients given ICTS had less rapid radiographic progression (RRP) after one year than those receiving IMT, despite more severe baseline disease characteristics. [6] Moreover, early disease outcome predicts normalized physical function, working status and remission later on in the disease course. [7] We hypothesized that in patients with early RA treated in daily practice ICTS would be more effective than IMT in preventing long-term radiological damage and set up this study to test this.

Patient and methods

Patients enrollment

At the Rheumatology department of the University Hospitals Leuven (UZL), consecutive patients with newly diagnosed DMARD-naïve RA were included in an observational cohort between 2001 and 2007. Patients included in clinical trials were excluded from the cohort. 74 patients from this cohort were selected in the current study because X-ray images of hands and feet at baseline, year one and year two were available.

This study was approved by the Ethics Committee of UZL and all patients consented to participate.

Treatment strategy

Based on expert opinion of two experienced rheumatologists (RW and PV) after informal evaluation of prognostic factors (rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), erosions and/or active disease), patients received ICTS or IMT. The ICTS scheme consisted of a modified COBRA (Dutch acronym Combinatie therapie Bij Rheumatoide Arthritis) regimen [8] of 2g sulphasalazine (SSZ) daily, 15mg methotrexate (MTX) weekly and a step-down dosage of oral prednisolone starting at 60mg, which is tapered in six weeks to 7.5 mg/d and discontinued after 28 weeks.

In IMT, initial DMARD choice was freely chosen by the treating physician.

Tight control

Patients were evaluated approximately every three months and treatment adjustments, if feasible and desirable, were made whenever the target, a 28joint disease activity score [DAS28 (CRP)] below 3.2, was not reached. Therapeutic changes were defined as discontinuing, changing or adding DMARDs or biologicals and were left to the discretion of the treating physician. Dose changes were not counted as therapy changes.

Demographics and disease characteristics

Demographics were registered at baseline and the following clinical characteristics were obtained at baseline, year one and year two: swollen/tender joint counts (TJC , SJC, TJC 28 and SJC 28), assessment scores by Visual Analogue Scales (VAS patient global-PGA, VAS physician global-PhGA, VAS pain and VAS fatigue), Health assessment questionnaire (HAQ), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Disease activity score based on CRP status [DAS28 (CRP)], good EULAR DAS response (if the DAS28 score is below 3.2 and dropped 1.2 points), clinically meaningful HAQ response (if the HAQ score dropped 0.22 points), DAS change and HAQ change were calculated from DAS28CRP and HAQ at year 1 or year 2 versus baseline. Remission was defined as a DAS28(CRP) score below 2.6.

Radiographic scoring

X-ray images were scored according to the modified Sharp/van der Heijde (SvdH) method[9] by three readers in consensus: two experienced musculoskeletal radiologists (LL and GVDS) and one clinical researcher (DDC). Radiographic damage was defined as a total Sharp score (TSS) higher than 0. TSS progression equal or higher than 5 units per year was considered RRP. Mean change in TSS, erosion and joint space narrowing score and the proportion of patients with RRP were compared between both groups.

Statistical analysis

Repeated measures analyses of variance (ANOVA) were used firstly to determine the within subject effect of treatment with a post-hoc Bonferroni correction on the whole group, on the ICTS patients and on the IMT patients and the interaction effect between time and treatment by Wilks'Lambda. Secondly, a repeated measures analyses of variance (ANOVA) was chosen to explore the effect of treatment on clinical and radiographic outcome variables with treatment strategy as a between subjects factor. Eta squared, a measure of the amount of the variation explained by the model, was used as a degree of effect size of ICTS over IMT. Variables were log transformed to correct for normality. Remission scores, DAS changes, proportion of good EULAR responders, HAQ change,

proportion of clinically meaningful HAQ responders, cumulative GCs dose, proportion of GC users were compared between IMT and ICTS at year 1 or year 2 with Chi square or Mann-Whitney U-tests.

All statistical tests were evaluated at the 0.01 significance level to control for multiple comparison. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0.

Results

Treatment Strategy

42 Patients received IMT while 32 started ICTS. At baseline, 26 patients in the IMT group received MTX monotherapy, 14 followed SSZ treatment, one got a combination of MTX with hydroxychloroquine (HCQ) and one started treatment with azathioprine. The patient who received a combination of MTX with HCQ was considered to be on monotherapy: HCQ was started before screening in our hospital, but stopped immediately after treatment initiation. The patient was then put on MTX monotherapy. After two years of treatment in the IMT arm, 37 patients received monotherapy, four a combination of DMARDs and one no DMARDs. At baseline, all ICTS subjects except one started the modified Cobra scheme. One patient received an adapted regime without MTX because of a pregnancy wish. After two years, 22 ICTS patients received monotherapy, four a combination of DMARDs, four a biological (Infliximab+MTX, Humira, Etanercept and Rituximab) and two no DMARDs.

The IMT group required 40 therapeutic changes (0.95 therapy changes/IMT patient) compared to 18 changes in the ICTS group (0.47 therapy changes/ICTS patient).

Glucocorticoid use

After one year, the mean ± SD cumulative GCs dose (in prednisolone equivalents) reached 2501 ± 306 mg in ICTS patients and 1041 ± 1198 mg in IMT patients ($p<0.001$). In the second year, the mean ± SD cumulative GCs dose was 333 ± 702 mg in the ICTS group and 355 ± 684mg in the IMT group ($p=0.895$). At any moment in the first year, 100% of the ICTS group used GCs compared to 62% in the IMT group ($p<0.001$). In the second year 19% of the ICTS group used GCs at any moment compared with 36% in the IMT group ($p=0.089$). Over the two year study period, the ICTS patients took a mean ± SD daily GCs dose of 3.3 ± 1.2 mg, while the IMT patients took 1.7 ± 2.0 mg ($p<0.001$).

Demographics

In the ICTS group, mean ± SD patient age was 50 ± 15 years at inclusion with a mean ± SD symptom duration of 8 ± 6 months and a mean disease duration of less than 1 ± 1 month. 69% of patients was female, 75% RF positive, 75% ACPA positive and 56% erosive. In the IMT group, mean ± SD patient age was 53 ± 17 years at inclusion with a mean ± SD symptom duration of 9 ± 8 months and a mean disease duration of less than 1 ± 1 month. 62% of patients was female, 69% RF positive, 68% ACPA positive and 38% erosive. Demographics did not differ between IMT and ICTS patients (data not shown).

Clinical evolution

At baseline, SJC and PhGA were significantly higher in the ICTS patients compared to the IMT patients. In absolute numbers, all other variables were also higher in the ICTS group. Thus ICTS patients were initially perceived to have a higher level of RA severity compared with IMT patients.

In both groups and in the total population, treatment had a statistically significant beneficial effect on all clinical characteristics except fatigue. Interaction between time and treatment was significant in PhGA and DAS28(CRP) (data not shown).

Table 1: Comparison of the clinical characteristics between the IMT and ICTS group

Clinical characteristics	Treatment group	n	Baseline	n	Year 1	n	Year 2	p-value	Effect size
Total TJC	**IMT**	42	11.71 ± 10.34	42	3.19 ± 4.62	42	4.88 ± 6.57	0.890	0,089
	ICTS	32	17.81 ± 10.05	32	4.47 ± 5.01	32	3.79 ± 4.88		
Total SJC	**IMT**	42	10.17 ± 7.15	42	2.26 ± 3.20	42	1.79 ± 2.60	0.002	0,278
	ICTS	32	15.44 ± 8.61	32	2.84 ± 4.05	32	3.28 ± 5.38		
TJC28	**IMT**	42	6.95 ± 6.08	42	1.50 ± 2.39	42	2.12 ± 3.09	0.270	0,048
	ICTS	32	10.03 ± 6.43	32	2.28 ± 3.03	32	3.09 ± 4.66		
SJC28	**IMT**	42	7.12 ± 5.13	42	1.67 ± 2.38	42	1.45 ± 2.02	0.019	0,195
	ICTS	32	9.19 ± 5.47	32	1.94 ± 2.56	32	2.41 ± 4.15		
ESR	**IMT**	42	35.76 ± 25.05	42	16.31 ± 17.78	41	16.83 ± 14.89	0.299	0,015
	ICTS	32	37.84 ± 23.03	32	12.47 ± 12.64	32	13.94 ± 14.89		
CRP	**IMT**	42	28.67 ± 34.81	42	6.49 ± 8.08	40	8.07 ± 10.02	0.516	0,066
	ICTS	32	28.97 ± 32.93	32	4.81 ± 6.89	32	5.60 ± 6.81		
PhGA (0-100)	**IMT**	37	32.84 ± 16.91	42	12.10 ± 10.57	41	12.05 ± 13.05	0.318	0,015
	ICTS	29	54.00 ± 15.57	32	15.75 ± 12.60	30	12.40 ± 13.05		
PGA (0-100)	**IMT**	39	50.31 ± 25.09	42	33.62 ± 21.66	42	37.71 ± 24.39	0.151	0,042
	ICTS	31	57.65 ± 24.36	32	31.25 ± 25.08	31	32.10 ± 26.04		
Pain (0-100)	**IMT**	38	49.92 ± 25.15	42	34.69 ± 22.07	42	34.69 ± 22.79	0.565	0,005
	ICTS	31	53.48 ± 23.67	32	33.19 ± 25.74	31	33.13 ± 29.50		
Fatigue (0-100)	**IMT**	38	41.08 ± 25.47	42	35.05 ± 24.92	42	33.60 ± 22.41	0.578	0,005
	ICTS	31	42.45 ± 25.76	32	34.91 ± 25.42	31	32.39 ± 26.12		
HAQ (0-3)	**IMT**	36	1.09 ± 0.81	42	0.54 ± 0.65	41	0.66 ± 0.72	0.727	0,004
	ICTS	30	1.11 ± 0.71	32	0.55 ± 0.68	32	0.76 ± 0.75		
DAS28 CRP	**IMT**	39	4.67 ± 1.14	42	2.70 ± 0.98	38	2.90 ± 1.09	0.605	0,004
	ICTS	31	5.23 ± 1.27	32	2.80 ± 1.11	30	2.64 ± 1.14		

IMT=Disease modifying anti rheumatic drug (DMARD) monotherapy; ICTS= initial combination therapy with steroids; TJC= tender Joint count; SJC= Swollen joint count; ESR = Erythrocyte sedimentation rate; CRP= C-reactive protein; PhGA = Physician global assessment; PGA = Patient global assessment; HAQ=Health assessment questionnaire; DAS28 = 28 joint Disease activity score. n = number of patients with available data at evaluation time. P-values represent the result of the statistical between subject comparison with repeated measures ANOVA between the IMT and ICTS group. Eta squared, a measure of the amount of the variation explained by the model, was used as a degree for effect size of ICTS over IMT.
Values given are mean $\pm$ SD. All tests were conducted at the 0.01 significant level.

Table 1 shows that this baseline difference between the two groups was rendered equal in the following two years with the exception of the swollen joint count, which remained slightly higher in the ICTS group.

At year one, both treatment groups achieved 50% remission. After two years of treatment, 37% of IMT patients and 60% of ICTS patients were in remission. The absolute DAS change was significantly higher in ICTS patients after two years of treatment. Table 2 describes these disease outcome parameters in more detail.

Table 2: Remission, change in DAS28 score, Good EULAR DAS response, change in HAQ score and clinically meaningful HAQ response in the total population, IMT and ICTS group

Period	Disease outcome	Total	n	IMT	n	ICTS	n	p-value
Year 1	**Remission**	50%	74	50%	42	50%	32	0.593
	Change in DAS28 (CRP)	2.14 ± 1.43	70	1.93 ± 1.03	39	2.40 ± 1.80	31	0.176
	Good EULAR DAS response	71%	71	68%	40	77%	31	0.257
	Change in HAQ score	0.55 ± 1.10	66	0.53 ± 1.14	36	0.58 ± 1.04	30	0.883
	Clinically meaningful HAQ response	66%	65	71%	35	60%	30	0.239
Year 2	**Remission**	47%	68	37%	38	60%	30	0.049
	Change in DAS28 (CRP)	2.22 ± 1.50	64	1.76 ± 1.33	35	2.77 ± 1.53	29	0.007
	Good EULAR DAS response	67%	64	60%	35	76%	29	0.140
	Change in HAQ score	0.37 ± 1.16	65	0.40 ± 1.17	35	0.34 ± 1.17	30	0.840
	Clinically meaningful HAQ response	59%	65	63%	35	53%	30	0.300

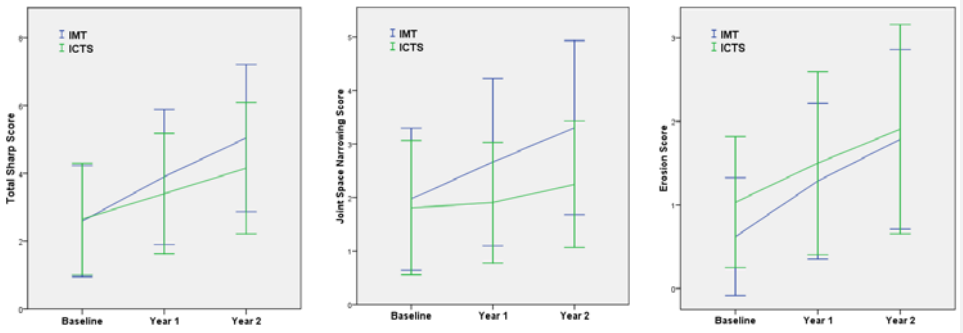
IMT=Disease modifying anti rheumatic drug (DMARD) monotherapy; ICTS= initial combination therapy with steroids; HAQ=Health assessment questionnaire; DAS28 = 28 joint Disease activity score.
Remission was defined as a DAS28 CRP score of lower than 2.6. Changes in HAQ and DAS28 score were calculated between year 1 or year 2 and baseline. A Good EULAR DAS response was defined as a DAS28 ≤ 3.2 with a DAS28 change >1.2. A clinically meaningful HAQ response was defined as a HAQ change >0.22. n = number of patients with available data at evaluation time. P-values represent the result of the statistical comparison with Chi-square tests or Mann-Whitney-U tests between the IMT and ICTS group.
Values given are percentages or mean ± SD. All tests were conducted at the 0.01 significant level.

Radiographic evolution

In the total population, 54% of the patients at baseline, 42% at year 1 and 34% at year 2 had no radiographic damage, defined as a TSS equal to 0. In the IMT group, 62% of the patients at baseline, 43% at year 1 and 33% at year 2 had no radiographic damage. In the ICTS group, 44% of the patients at baseline, 41% at year 1 and 34% at year 2 had no radiographic damage. Progression is thus well controlled in the majority of patients.

Figure 1 displays the erosive evolution and radiologic scores over two years of the IMT and ICTS patients. Both groups showed similar progression. However, a trend for less structural damage in the long term in favor of ICTS was observed.

Figure 1: Comparison of the radiologic evolution between the IMT and ICTS group over two years



Period	Total Sharp Score		Joint Space Narrowing Score		Erosion Score	
	IMT	ICTS	IMT	ICTS	IMT	ICTS
Baseline	2.60 ± 5.26	2.66 ± 4.57	1.98 ± 4.26	1.81 ± 3.48	0.62 ± 2.26	1.03 ± 2.18
Year 1	3.90 ± 6.40	3.41 ± 4.93	2.67 ± 5.02	1.91 ± 3.12	1.29 ± 3.00	1.50 ± 3.04
Year 2	5.05 ± 6.96	4.16 ± 5.37	3.31 ± 5.22	2.25 ± 3.27	1.79 ± 3.45	1.91 ± 3.47
p-value	0.732		0.486		0.697	
Effect size	0,002		0,006		0,002	

IMT=Disease modifying anti rheumatic drug (DMARD) monotherapy; ICTS= initial combination therapy with steroids. Values given are mean ± SD. P-values represent the result of the statistical between subject comparison with repeated measures ANOVA between the IMT and ICTS group. Eta squared, a measure of the amount of the variation explained by the model, was used as a degree for effect size of ICTS over IMT. All tests were conducted at the 0.01 significant level.

Rapid radiographic progression

- RRP at year 1

RRP was found in four patients between baseline and year one: three IMT patients and one ICTS patient. All three IMT patients started initially MTX monotherapy. In the first year, all three received GCs and the dose was increased for two patients. In the second year two IMT patients switched to another classic DMARD and all received further GCs. The ICTS patient with RRP was given SSZ without dosage changes or GC use after the initial Cobra scheme.
From these four patients with RRP in year one, none developed RRP between year one and year two.

- RRP between year 1 and year 2

RRP between year one and year two was found in four additional IMT patients, all on SSZ initial monotherapy and in one other ICTS patient. Four out of five were erosive at baseline. These IMT patients all switched to MTX during the second year. They were young females with a mean ± SD age of 31 ± 9 years. Two displayed a pregnancy wish. The three youngest were ACPA positive. However, these four patients displayed no high scores at baseline for the joint counts, DAS28(CRP) score, ESR/CRP status and PhGA, and were thus perceived as low risk.

- RRP over 2 years

Four patients had a change of ≥10 TSS units over two years. Three of these patients belonged to the IMT group and one to the ICTS group. Remarkably, three out of these four patients had already developed RRP during the first year but made no further radiographic progression in the second year.

Discussion

The aim of this study was to evaluate the clinical and radiologic evolution of patients with early RA treated with ICTS and IMT in a tight control setting in daily practice over a two year follow-up period.

Treatment Strategy

In daily practice, experts will logically choose a more intensive therapy for more severe RA patients. [10] Our observational study showed that this choice was not always ideal in all cases. More IMT patients developed RRP despite lower RA severity and radiographic damage at baseline. Besides, ICTS patients achieved higher remission rates and DAS change over two years, although disease characteristics and clinical outcomes were equal after one year.

Additionally, this study shows that a less intensive initial approach leads to more therapy changes reflecting the treating physician's difficult and time consuming search for an optimal treatment schedule.

Tight Control

Our study highlights the potential of tight control to achieve remission and to prevent structural progression over two years. This confirms previous findings where tight control in daily practice was shown more effective in achieving remission after one year. [11] Radiologic progression is effectively halted by a DAS driven approach in a TC setting in clinical practice. The majority of patients didn't have any or minimal radiological progress and both IMT and ICTS patients with RRP after one year showed minimal radiographic progression in the second year.The TC setting, without a strict treatment protocol, gives the rheumatologist more flexibility in tailoring the right medication for a patient in a timely fashion. This approach could diminish differences in effect between ICTS and IMT strategies in contrast to what can be observed in trials. [2-4, 8] The impact of adapting a treatment more frequently deserves additional attention from a patient perspective. Dealing with extra-therapeutic stressors, e.g. disappointments in therapy outcome or fear for novel drugs, should not be neglected.

Clinical evolution

The higher proportion of patients with an ICTS regimen in remission after two years is remarkable. Firstly, because IMT patients were perceived as having a less severe RA profile at baseline. Secondly, because ICTS and IMT patients had equal rates of remission at year 1. Finally because a similar tight control approach was applied in both groups after the induction phase.

Radiographic evolution

A trend towards less radiographic progression in the ICTS patients compared with the IMT patients was detected. This effect can partially be explained because no IMT patients versus 4 ICTS patients received any biological treatment. Physicians were possibly more strict in applying the TC principle in ICTS patients whom they considered to have a more severe disease profile. Furthermore, the initial intensive use of GCs in the first year by ICTS patient could protect against radiographic progression. [12]

In general, radiographic progression in our total population over two years was lower than what is considered to be clinically relevant. [13, 14]

Rapid radiographic progression

In this study, only one ICTS patient per year developed RRP out of 32 patients versus three IMT patients in the first year and four in the second year out of 42 patients.

Four notably young female IMT patients, considered to be at low risk despite a majority being ACPA positive [15], were initially treated with SSZ monotherapy but developed RRP in the second year. The two youngest patients had an active pregnancy wish. Therefore, physicians were possibly inclined to choose a more conservative treatment. It could be that this approach influenced RRP development. Thus, the risk of RRP is underestimated in certain patient groups, which is translated in conservative therapy choices.

Limitations

This study is a small sized observational cohort study and not a randomized clinical trial. No strong causality can be shown in this setting because of the less controlled environment and patient diversity. For example, the lack of medication protocol biases therapy comparison. The fact that four ICTS patients and no IMT patients received biologicals, illustrates this problem. Furthermore, the more severe RA profile of the ICTS patients, caused by leaving the treatment choice to an expert, gave the ICTS group the possibility to clinically improve more than the IMT group. Moreover, the small size of our population plus the occurrence of missing data, although only in a minority of cases, limits the ability to demonstrate true differences. Missing variables occurred randomly and were infrequent. Conclusions should be regarded with caution.

An important advantage of our approach is the lack of selection bias in the absence of in- and exclusion criteria and the possibility to extrapolate the results to clinical practice.

Conclusion

Both initial combination therapy with steroids and initial monotherapy prevent radiologic progression over two years, when applying the tight control principle in the daily practice of a Belgian academic hospital. ICTS appears to be more effective than IMT because of higher sustained remission rates with less therapy changes. In specific cases such as a pregnancy wish, physicians underestimate or ignore disease severity, which puts patients at risk for RRP.

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CHAPTER 3

Optimal intensive treatment

Page 86 Verschueren P*, De Cock D*, Corluy L, Joos R, Langenaken C, Taelman V, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. Annals of the rheumatic diseases. 2015;74(1):27-34.

Page 108 Verschueren P*, De Cock D*, Corluy L, Joos R, Langenaken C, Taelman V, et al. Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early Rheumatoid Arthritis: week 16 results from the randomized multicenter CareRA trial. Arthritis research & therapy. 2015;17(1):97.

Page 123 Verschueren P*, De Cock D*, Corluy L, Joos R, Langenaken C, Taelman V, et al. Efficacy and safety of different remission induction strategies combining synthetic DMARDS with or without glucocorticoid bridging for early rheumatoid arthritis (CareRA): 1 year results of a randomized pragmatic superiority trial (in draft)

*Verschueren P and De Cock D share a first-authorship

Methotrexate in Combination with Other DMARDs is not superior to Methotrexate alone for Remission Induction with moderate to high dose Glucocorticoid Bridging in early Rheumatoid Arthritis after 16 weeks of treatment: the CareRA trial.

Abstract

Objectives: To compare the efficacy and safety of intensive combination strategies with glucocorticoids (GCs) in the first 16 weeks (W) of early RA (eRA) treatment, focusing on high-risk patients, in the CareRA trial.

Methods: 400 DMARD naïve eRA patients were recruited and stratified into high or low-risk according to classical prognostic markers. High-risk patients (n=290) were randomized to 1/3 treatment strategies: COBRA Classic (MTX+ Sulphasalazine + 60mg prednisone tapered to 7.5mg daily from W7), COBRA Slim (MTX + 30mg prednisone tapered to 5 mg from W6), and COBRA Avant-Garde (MTX + Leflunomide + 30mg prednisone tapered to 5 mg from W6). Treatment modifications to target low disease activity were mandatory from W8, if desirable and feasible according to the rheumatologist. The primary outcome was remission (DAS28(CRP) <2.6) at W16 (ITT analysis). Secondary endpoints were good EULAR response, clinically meaningful HAQ response and HAQ equal to zero. Adverse events (AEs) were registered.

Results: Data from 98 Classic, 98 Slim and 94 Avant-Garde patients were analyzed. At W16, remission was reached in 70.4% Classic, 73.6% Slim and 68.1% Avant-Garde patients (p=0.713). Likewise, no significant differences were shown in other secondary endpoints. However, therapy-related AEs were reported in 61.2% of Classic, in 46.9% of Slim and in 69.1% of Avant-Garde patients (p=0.006).

Conclusion: For high-risk eRA, MTX associated with a moderate step-down dose of GCs was as effective in inducing remission at W16 as DMARD combination therapies with moderate or high step-down GC doses and it showed a more favorable short-term safety profile.

Introduction

While in the past patients with early Rheumatoid Arthritis (eRA) were treated conservatively, current guidelines recommend treating high-risk patients intensively, early and to target (1-3). A lot of interesting and important pioneering work has already been done but many questions regarding the optimal dosage and combination of medication in the management of eRA patients remain unaddressed (4).

Trials using early intensive combination strategies with classical Disease Modifying Anti Rheumatic Drugs (DMARDs) and glucocorticoids (GCs) gave rise to the ‘’early window of opportunity” theory (5-10). This implies that if intensive treatment is initiated early in the disease process and disease activity is rapidly controlled, more patients will go into long-term remission with better functional and radiographic outcomes later on (11-16). Discussion still exists about the optimal way to rapidly induce remission at the individual patient level. Some patients might do equally well on Methotrexate (MTX) monotherapy and even in case of insufficient response, intensifying to triple DMARD therapy or a combination with a biological can rescue patients later on (17). A delay in optimal disease control might indeed not necessarily result in worse outcomes at standard evaluation time points, but unfortunately doesn’t take into account the cumulative disease activity patients have to suffer before arriving at these endpoints. This illustrates that the patient perspective is still understudied in traditional eRA trials.

Guidelines suggest adapting treatment according to prognostic factors (1-3). Unfortunately, this doesn’t guarantee a favorable outcome in daily practice (18). Until better prediction models become available, the most effective approach to utilize the window of opportunity is to combine classical DMARDs with rapid remission inducing agents like GCs or biologicals.

GCs are commonly used to bridge the onset of the therapeutic effect of DMARDs, to rapidly control inflammation and to prevent radiographic damage (19-21). During the difficult initial treatment weeks, GCs can relieve pain, stiffness and

disability, allowing patients to take up again their role in society more rapidly, and potentially preventing chronic disease behavior. The perception on GCs remains however ambiguous, in both the patient's and the physician's mind. Thus many rheumatologists hesitate to prescribe GCs due to fear for side effects (22, 23). Little is yet known about the optimal initial dose, treatment duration and administration route (24).

Ample evidence exists that compared to MTX monotherapy, biologicals combined with MTX are more efficacious in eRA. Unfortunately, insufficient clarity exists if these agents can be used as remission induction agents in bridging strategies just as well as GCs, since most trial protocols led to persistent biological use after the induction phase (8, 9, 25-27). Moreover, TNF blocking agents didn't demonstrate superior efficacy compared to induction regimes with GCs (28). Thus, administering GCs could avoid or postpone starting expensive long-term biological therapy (29).

The debate on the ideal DMARD content of initial RA treatment strategies is still ongoing (30, 31). Triple therapy (MTX, Sulphasalazine (SSZ) and Hydroxychloroquine (HCQ)), COBRA (Combination therapy for early Rheumatoid Arthritis)-like schemes (MTX±SSZ+GCs) or other DMARD combination therapies show excellent clinical efficacy compared to monotherapy (5-8, 17, 32-37). However, studies comparing different intensive treat-to-target regimens of classical DMARDs associated with a remission-inducing agent are scarce.

The aim of the current study was to compare in high-risk eRA patients the efficacy and safety of different initial DMARD combinations and GC bridging schemes, 16 weeks after initiation.

Patients and Methods

The CareRA study

CareRA (Care in early RA - EudraCTnumber: 2008-007225-39) is a prospective 2 year investigator-initiated multicenter Randomized Controlled Trial (RCT) rooted in daily practice. The trial is conducted in 13 Flemish rheumatology centers: 2 academic centers, 7 general hospitals and 4 private practices.

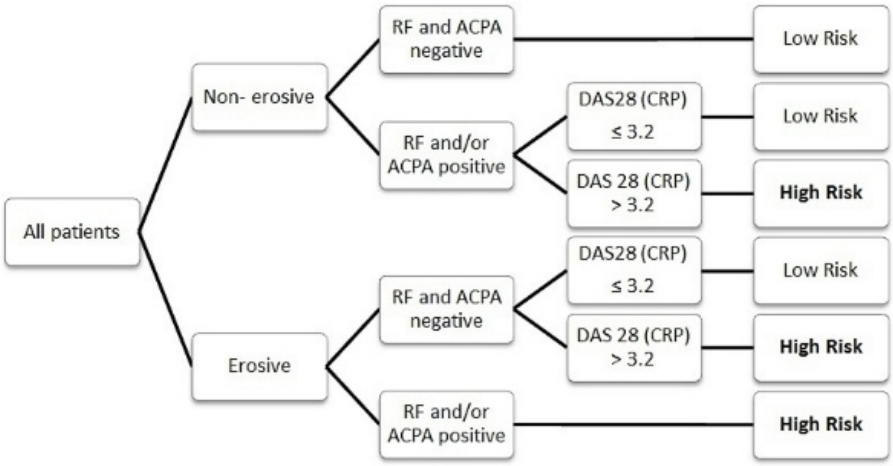
This study was approved by the Ethics Committee (EC) of the University Hospitals Leuven after consultation of the local ECs. All patients gave written informed consent before inclusion.

Patients

Patients with RA, as defined by the American College of Rheumatology (ACR) 1987 revised criteria, were recruited between January 2009 and May 2013. The main inclusion criteria were having a disease duration ≤1 year and being DMARD and GCs treatment naïve. Disease duration was defined as time elapsed between RA diagnosis and treatment initiation. Patients having contra indications for intensive treatment combinations with GCs as judged by the treating rheumatologist were excluded. See supplement 1 for a full list of exclusion criteria.

Patients were allocated to a high-risk group based on an algorithm constructed with classical RA prognostic factors: erosions, Rheumatoid Factor (RF) and/or anti-citrullinated protein antibody (ACPA) and disease activity score based on C-reactive protein (CRP) status [DAS28 (CRP)] at screening. (figure 1)

Figure 1: Classification of patients in high or low risk according to classic prognostic factors



RF= Rheumatoid Factor, ACPA= Anti-citrullinated protein antibody, DAS28 (CRP) = 28 joint disease activity score calculated with C-reactive protein.

Design

After risk allocation, high-risk patients were randomized into 1/3 treatment arms:

- COBRA CLASSIC: 15mg MTX weekly, 2g SSZ daily and a weekly step-down scheme of oral GCs (60-40-25-20-15-10-7.5mg prednisone) This scheme has a higher dose of MTX than the original cobra schedule, based on experience in daily clinical practice. (5, 35)
- COBRA SLIM: 15mg MTX weekly with a weekly step-down scheme of oral GCs (30-20-12.5-10-7.5-5mg prednisone).
- COBRA AVANT-GARDE: 15mg MTX weekly, 10mg Leflunomide (LEF) daily and a weekly step-down scheme of oral GCs (30-20-12.5-10-7.5-5mg prednisone).

The GC dose was tapered down weekly except for the lowest dose (7.5mg in COBRA CLASSIC and 5mg in the other arms), which was maintained until week (W) 28. Then, GCs were tapered on a weekly basis by leaving out 1 daily dose each week over a period of 6 weeks, until complete discontinuation. Prophylactic treatment including oral folic acid, calcium and vitamin-D supplements was prescribed to all patients. Furthermore, all patients received face-to-face education and info-material (leaflet, DVD and website) about the disease as well as on the proposed treatment at screening. Additional information was given on demand.

A treat-to-target approach was used in a tight control setting (38), aiming for a DAS28(CRP) ≤3.2 (39). If patients failed to reach this target, treatment adjustments were made according to protocol from week 8 onwards. Treating rheumatologists had the option not to adapt treatment, but in that case had to motivate their decision based on a predefined list of specific clinical conditions. Other treatment adjustments not stated in the protocol could not be implemented by the treating physician. The first adjustment in all treatment arms was a weekly increase in MTX dose to 20mg. If necessary a second adjustment could be made from 8 weeks after the first adjustment. The second adjustment depended on the treatment arm: a SSZ dose increase to 3g daily in COBRA CLASSIC, a LEF addition of 10mg daily in COBRA SLIM or a LEF dose increase to 20mg daily in COBRA AVANT-GARDE. If patients did not reach the target after 2 predefined

treatment adjustments during the first year , this was considered a strategy failure for efficacy reasons.

Intramuscular and intra-articular GC injections were allowed maximally every 8 weeks, but not within 4 weeks preceding W16. Concomitant therapy with NSAIDS and analgesics was allowed and registered.

Assessment

Patients were assessed at screening, baseline, W4, W8 and W16. Maximally four weeks were allowed between screening and baseline. In case a treatment adjustment was required according to the protocol at W8, an optional visit was performed at W12. Demographics were registered at screening and clinical parameters, DAS28(CRP) and HAQ at every visit. (table 1)

Safety and toxicity

At each visit, patients were asked about any adverse events (AE) and medication changes. Each reported AE was registered and evaluated in relation to therapy, seriousness and severity by the treating rheumatologist. In case of toxicity, the protocol predefined schemes for tapering/interrupting the assigned treatment strategy. If toxicity was persistent, this was considered a strategy failure for safety reasons.

Outcomes

The primary outcome of this study was the proportion of patients in remission (DAS28(CRP)<2.6) at W16. Secondary outcomes were the proportion of good EULAR responders (DAS28(CRP) change>1.2 and DAS28(CRP)≤3.2), the proportion of patients having a clinically meaningful improvement of the HAQ (HAQ change>0.22) and the proportion of patients having a HAQ equal to zero at W16.

Statistical analysis

The study was designed as a superiority analysis of CLASSIC versus SLIM and AVANT-GARDE versus SLIM. Sample-size calculation was based upon the proportion of patients in remission at W16. Eighty-five patients per treatment arm

were required for a power of 80% and significance level of 0.05, starting from an estimated clinically relevant difference in effect size of 20%. All patients starting treatment were analyzed.

Missing data were handled as follows. Screening variables were used to impute missing baseline variables and vice versa. A maximum likelihood model (by the Expectation-Maximization algorithm) was applied to impute missing data needed to calculate the DAS28(CRP) at W4, W8 and W16.

An intention-to-treat (ITT) analysis was performed by χ^2 or Kruskal-Wallis test, when appropriate. Area Under the Curve (AUC) analysis was used to evaluate the DAS28(CRP) over time. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 20. A p-value <0.05 was considered statistically significant.

Results

A total of 400 patients were screened and 380 patients were included in CareRA. 75% of these patients were included in non-university centers. No differences in demographic and clinical characteristics were observed between screened and included patients. 290 patients were allocated to the high-risk group and randomly assigned to treatment in the COBRA CLASSIC (98), COBRA SLIM (98) and COBRA AVANT-GARDE (94) arm. Randomization resulted in similar baseline characteristics between groups. (table 1)

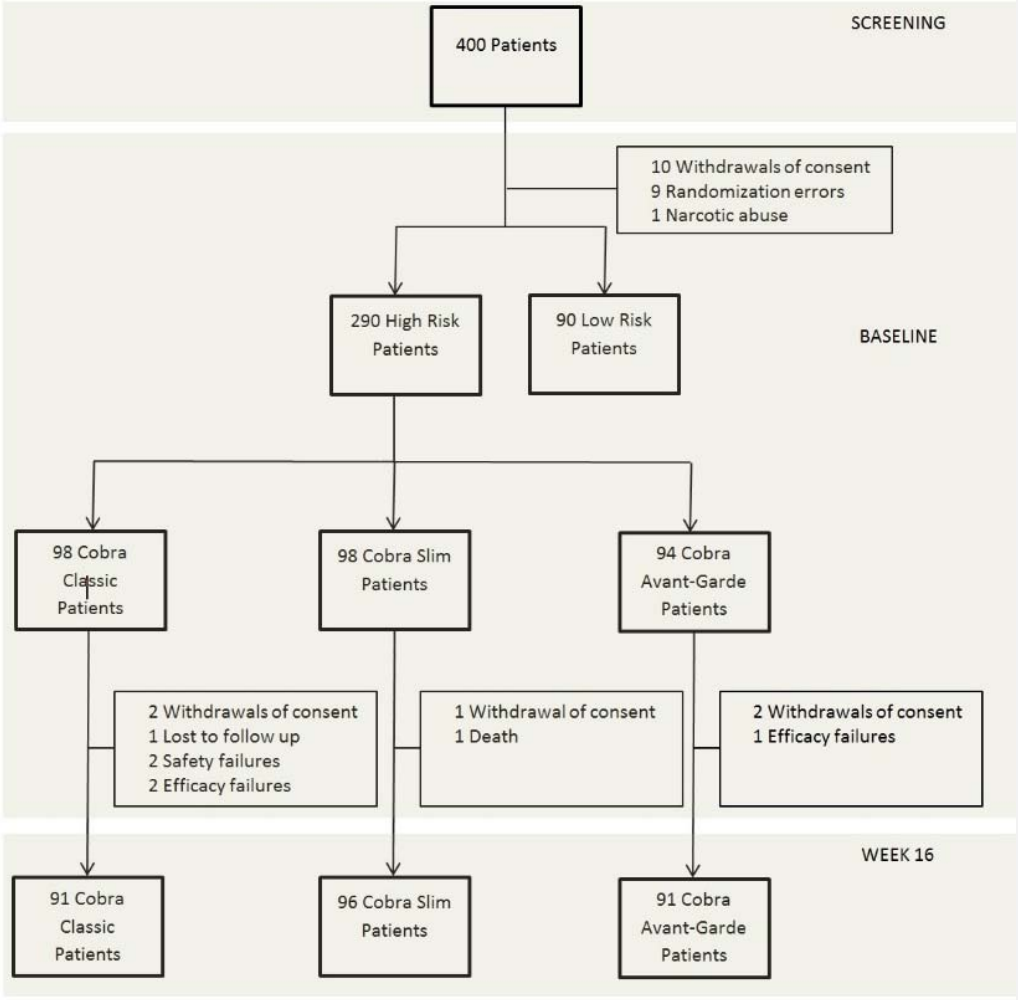
Figure 2 describes the patient disposition from screening until week 16.

Table 1: Patients' characteristics at baseline per treatment arm

	Cobra Classic	Cobra Slim	Cobra Avant-Garde
Number of patients	98	98	94
Age (years)	53.2 ± 11.9	51.8 ± 13.1	51.2 ± 12.8
BMI (kg/m²)	26.0.99 ± 4.3	26.8 ± 4.2	26.5 ± 4.2
Gender (female)	65.3%	64.3%	69.1%
Smoking Status (ever)	57.1%	59.2%	60.6%
Alcohol Intake (yes)	55.1%	56.1%	54.3%
Symptom Duration (weeks)	33.8 ± 35.5	33.2 ± 38.2	44.2 ± 65.6
Comorbidities at screening (yes)	72.4%	74.5%	64.9%
Morning Stiffness (yes)	74.5%	68.4%	58.4%
RF (yes)	79.6%	83.7%	75.5%
ACPA (yes)	77.6%	79.6%	77.7%
Erosions (yes)	32.7%	32.7%	34.0%
Total TJC	14.7 ± 9.5	13.7 ± 8.2	14.0 ± 9.0
Total SJC	11.9 ± 8.9	10.8 ± 6.5	10.5 ± 6.8
PGA (0-100)	59.5 ± 21.7	56.2 ± 21.7	54.5 ± 24.3
Pain (0-100)	59.5 ± 23.6	56.5 ± 21.9	56.9 ± 23.88
Fatigue (0-100)	50.6 ± 26.0	49.0 ± 21.3	48.68 ± 23.78
PhGA (0-100)	54.7 ± 18.5	53.1 ± 18.1	51.8 ± 18.2
ESR	33.59 ± 25.2	32.1 ± 23.3	25.18 ± 17.7
CRP	19.7 ± 28.9	21.5 ± 33.3	15.1 ± 20.0
DAS28(ESR)	5.4 ± 1.3	5.2 ± 1.2	5.0 ± 1.3
DAS28(CRP)	5.0. ± 1.2	4.9 ± 1.1	4.7 ± 1.2
HAQ (0-3)	1.2 ± 0.7	0.98 ± 0.69	0.99 ± 0.64

BMI= Body mass index; Symptom duration = time elapsed between onset of symptoms and start of treatment; Disease duration= time elapsed between diagnosis of RA and start of treatment; Morning stiffness = being stiff in the morning for at least 45 minutes; RF= Rheumatoid factor; ACPA= Anti-citrullinated protein antibody; PGA= Patient global assessment; PhGA= Physician global assessment; TJC= Tender joint count; SJC= Swollen joint count; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28= 28 joint Disease activity score; HAQ= Health assessment questionnaire. Data is presented as mean ± standard deviation or as percentages.

Figure 2: Patient disposition flowchart



Efficacy

Primary outcome

Remission was achieved in 70.4% (68/98) COBRA CLASSIC patients, 73.5% (72/98) COBRA SLIM patients and 68.1% (64/94) COBRA AVANT-GARDE patients (p =0.713) at W16. (figure 3a)

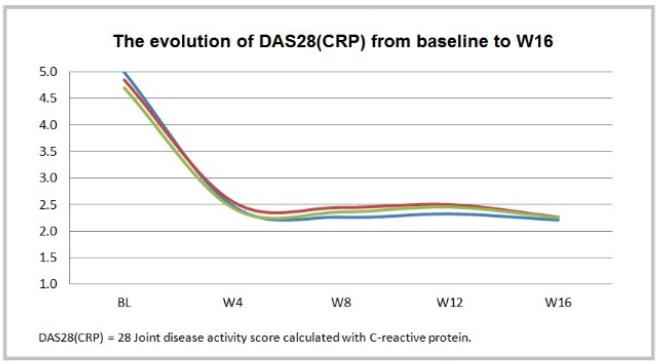
Figure 3 Remission and Disease Activity over 16 weeks

3a: The proportion of patients in remission per treatment arm at week 4, 8 and 16

	Cobra Classic	Cobra Slim	Cobra Avant-Garde	p-value
	98	98	94	
W4	63 (64.3%)	60 (61.2%)	60 (70.4%)	0.892
W8	64 (65.3%)	61 (62.2%)	65 (73.5%)	0.602
W16	69 (70.4%)	72 (73.5%)	64 (68.1%)	0.713

Remission was defined as DAS28(CRP) <2.6; DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein. The proportion of patients per treatment arm was compared via χ^2 testing and no statistically significant differences were found.

3b: The area under the curve of DAS28(CRP) per treatment arm during 16 weeks of treatment



DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein.

Secondary outcomes

At W16, a good EULAR response was reached in 79.6% of CLASSIC patients, 79.6% of SLIM patients and 76.6% of AVANT-GARDE patients (p =0.844). A clinically meaningful HAQ response was reached in 84.7% of CLASSIC patients, 86.7% of SLIM patients and 76.6% of AVANT-GARDE patients (p =0.271). HAQ was equal to zero in 45.9% of CLASSIC patients, 42.9% of SLIM patients and 48.9% of AVANT-GARDE patients (p =0.700). (table 2)

Table 2: Clinical outcomes at week 16 per treatment arm

	Cobra Classic	Cobra Slim	Cobra Avant-Garde	p-value	Δ between Classic vs Slim (95% C.I.)	Δ between Avant-Garde vs Slim (95% C.I.)
Number of patients	98	98	94			
DAS28 (CRP) Change	2.8 ± 1.2	2.6 ± 1.2	2.4 ± 1.3	0.140	0.2 (-0.13 to 0.52)	-0.2 (-0.49 to 0.21)
Remission	70.4%	73.5%	68.1%	0.713	-3.1% (-15.4% to 9.5%)	-5.4% (-18.0% to 7.4%)
Low Disease Activity	84.7%	86.7%	87.2%	0.863	-2.0% (-12.0% to 7.9%)	0.5% (-9.3% to 10.2%)
Good Eular Response	79.6%	79.6%	76.6%	0.844	0.0% (-11.3% to 11.3%)	-3.0% (-14.7% to 8.7%)
Moderate Eular Response	98.0%	95.9%	93.6%	0.320	2.1% (-3.6% to 8.2%)	-2.3% (-9.6% to 4.6%)
HAQ Change	0.8 ± 0.6	0.6 ± 0.6	0.7 ± 0.6	0.081	0.2 (0.02 to 0.37)	0.1 (-0.17 to 0.19)
Clinically Meaningful HAQ Change	84.7%	76.5%	76.6%	0.271	8.2% (- 3.0% to 19,1%)	0.1% (-11.9% to 12.0%)
HAQ = 0	45.9%	42.9%	48.9%	0.700	3.0% (-10.7% to 16.6%)	6.0% (-7.9% to 19.7%)

DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein; DAS28(CRP) change = DAS score on baseline minus DAS score on week 16; Remission was defined as DAS28(CRP) <2.6; Low Disease Activity was defined as DAS(CRP) ≤3.2; Good Eular Response was defined as low disease activity with a DAS28(CRP) change >1.2. Moderate Eular Response was defined as DAS28(CRP) change >1.2 or a DAS28(CRP) ≤5.1 and a DAS28(CRP) change between 0.6 and 1.2; HAQ = Health Assessment Questionnaire; HAQ change = Baseline HAQ minus week 16 HAQ; clinically meaningful HAQ change was defined as a HAQ change >0.22. Data is presented as mean ± standard deviation or as percentages. Statistical analysis was performed by χ^2 or Kruskal-Wallis test. A p-value <0.05 was considered statistically significant. Δ = difference; C.I. = Confidence Intervals (calculated by the Newcombe method for differences between proportions). DAS28(CRP) was imputed in 7 out of 98 Classic, 2 out of 96 Slim and 4 out of 94 Avant-Garde patients. HAQ was imputed in 7 out of 98 Classic, 2 out of 96 Slim and 5 out of 94 Avant-Garde patients.

Likewise, complete case analysis (without missing data imputation) of the primary and secondary outcomes revealed no significant differences between the 3 treatment arms (data not shown).

Area Under the Curve

The mean ± SD AUC for DAS28(CRP) from baseline to W16 was 10.66 ± 3.41, 11.05 ± 3.39 and 10.72 ± 2.96 for the CLASSIC, SLIM and AVANT-GARDE respectively (p=0.521). (figure 3b)

Treatment adaptations according to protocol

During the first 16 weeks of therapy, treatment adaptations were performed in 19.4%, 22.4% and 14.9% in the CLASSIC, SLIM and AVANT-GARDE arm respectively (p=0.407). Of these patients requiring treatment adaptations at W8, 50,0%, 87,5% and 60,0% in the CLASSIC, SLIM and AVANT-GARDE arm respectively reached the low disease activity target at W16 (p=0.086). Of 61 patients requiring per protocol treatment adaptation at week 8, 39% (24/61) had no change in therapy because of contraindications or because the treating physician judged the disease sufficiently controlled. These 24 patients received no other medication and stayed on the initial strategy without treatment adaptation. Intra-articular GC injections were given in 3.1% of CLASSIC patients, 5.1% of SLIM patients and 5.1% of AVANT-GARDE patients (p=0.703).

Safety

Therapy related AEs were registered in 171 out of the 290 patients (59%) during the first 16 weeks of treatment. These were reported in 61.2% of CLASSIC, in 46.9% of SLIM and in 69.1% of AVANT-GARDE patients (p=0.006). The total number of AEs related to CLASSIC, SLIM and AVANT-GARDE treatment was 148, 70 and 130 respectively, with a similar distribution for discomfort and toxicity. (table 3)

Table 3: Number of adverse events per treatment arm during 16 weeks of treatment

		Cobra Classic	Cobra Slim	Cobra Avant-Garde
Number of patients		91	96	91
AE related to therapy		148	70	130
Type related AE	Discomfort	111	50	96
	Toxicity	27	10	23
	Infection	5	3	5
	Others	4	7	6
	Surgery	1	0	0
Severity of related AE	Mild	121	64	103
	Moderate	23	5	21
	Severe	4	1	6
Serious AE		2	1	3

AE = Adverse event

Discussion

In eRA patients with unfavorable classical prognostic factors such as RF, ACPA, erosions and/or high disease activity, MTX associated with a moderate step-down dose of GCs was as effective as DMARD combination therapies with moderate or high step-down GC doses, for remission induction at 16 weeks. Furthermore, the short-term safety profile of MTX associated with a moderate step-down dose of GCs was more favorable.

This finding has 2 implications. Firstly, in association with a moderate or high GC dose, the combination of MTX with other DMARDs does not seem to be more effective compared to MTX alone, at least in the early treatment stage. Until now only few studies have addressed the question if DMARD combinations are superior to MTX monotherapy independent from additional GC bridging in eRA (7, 32-34). The tREACH trial showed that DMARD combination was better than

MTX monotherapy, both in association with low dose GC bridging. In our trial, the COBRA-like moderate or high dose GC scheme bridged the time lag before full DMARD efficacy, probably erasing any difference between the different DMARD schedules. As a consequence, less medication is needed over time, which might impact adverse events and possibly also patients' adherence to treatment. The tight control setting could also correct swiftly for any suboptimal treatment regimen, explaining some of the good efficacy of COBRA SLIM. However, only MTX dose adjustment and no step up to combination therapy could be implemented before W16. Furthermore, the proportion of treatment adjustments between the three arms wasn't significantly different.

Secondly, a high-dose GC scheme starting at 60mg prednisone does not seem to improve early clinical outcomes compared with a moderate-dose scheme starting at 30mg prednisone, regardless of the DMARD strategy used. Thus, a lower cumulative GC dose is still equally effective, perhaps avoiding long-term AEs. Furthermore, the possibility to use a lower dose of GCs, while having the same efficacy could benefit the implementation of COBRA-like strategies. Rheumatologists appear more reluctant to administer complex therapies with high dosages of GCs (22, 23, 40-42), although we showed that this approach is feasible in daily practice (35). Den Uyl et al reported similar results comparing an attenuated COBRA regimen with the original one in a moderately active eRA population (36). However, this study lacked decisive evidence, the MTX dose in the classical scheme was suboptimal, and the glucocorticoid scheme in the attenuated COBRA version was cumulatively comparable to the classical one.

Many rheumatologist use low dose GCs in association with DMARDS for eRA in daily practice, much to their own and their patients' satisfaction. They have however doubts about the need for higher GC dosages and prolonged use. The potential advantage of a COBRA-like schedule over low-dose GCs is two-sided . Firstly, a high or moderate dose could have a more radical biological effect on the disease process favoring "real" remission induction (43). Low-dose GCs show only a slow genomic effect, while higher dosages show both slow genomic and faster non-genomic effects (44, 45). Secondly, compared to using GCs only short

term and discontinuously, it can be more effective to bridge systematically the entire time window before maximum DMARD efficacy, taking up to six months (46-48). DMARD combinations could therefore have a short-lived advantage over DMARD monotherapy in trials using GCs not systematically, at a too low dose or for a too short period of time (32, 33, 37, 46).

The analysis of the area under the curve of disease activity reinforced the study findings at every visit, illustrating that the disease burden was the same during the first 16 weeks of treatment over the three treatment arms. A delayed targeted therapy as proposed by others (17) would result in a much higher cumulative disease activity. This study only presents the first 16 weeks of the CareRA trial, but this initial treatment period, the so-called 'window of opportunity' is crucial for longer-term outcome at the biological and probably also at a psychosocial level (15, 49). Long-term disease control and patient reported outcomes after one and two years are awaited in CareRA.

The safety analysis strengthened the efficacy outcomes further. The proportion and number of related AEs was comparable in CLASSIC and AVANT-GARDE, while SLIM patients had half the related AEs. GC dosage doesn't make any difference in the frequency or type of related AEs at this stage. Remarkable are the comparable number of AEs of the combination therapies with different GC dose, underscoring again the prejudice against GC dosage and lack of knowledge of GC side effects.

The first two limitations are related to the design of this study, although unavoidable in a pragmatic trial aiming to reflect daily clinical practice. Firstly, medication adherence wasn't measured. However, if adherence was lower in a certain trial arm, the same could be expected from this treatment regimen in daily clinical practice. Secondly, no blinding was implemented. Rheumatologists could have been biased towards a certain therapy and therefore report less therapy related AEs. Certain patients could also be more motivated for certain treatment regimens than for others.

Another limitation was the superiority design of this study. We opted for this design because in a non-inferiority trial the number of patients needed would be doubled. Hence, we can only state that Cobra Classic and Cobra Avant-Garde are non-superior to Cobra Slim, which is not the same as claiming non-inferiority.

In conclusion, the data presented are positioning classical MTX therapy with bridging GCs at a lower dose than in the original COBRA study as a highly effective and safe remission induction therapy in more than 70% of high-risk eRA patients and this in a close to daily practice setting applying a treat-to-target strategy

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Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early Rheumatoid Arthritis: week 16 results from the randomized multicenter CareRA trial

Abstract

Introduction: Considering a lack of efficacy data in patients with early Rheumatoid Arthritis (eRA) presenting without classical poor prognosis markers, we compared methotrexate (MTX) with or without step-down glucocorticoids in the Care in early RA (CareRA) trial.

Methods: Disease Modifying Anti-Rheumatic Drugs (DMARDs) naïve eRA patients were stratified into a low-risk group based on prognostic markers including non-erosiveness, Anti-Citrullinated-Protein Antibodies (ACPA) and Rheumatoid Factor (RF) negativity and low disease activity (DAS28(CRP)≤3.2). Patients were randomized to 15mg MTX weekly (MTX-TSU) or 15mg MTX weekly with prednisone bridging, starting at 30mg and tapered to 5mg daily from week 6 (Cobra Slim). A tight step-up (TSU) approach was applied. Outcomes were DAS28(CRP) remission, cumulative disease activity, Health Assessment Questionnaire (HAQ) and adverse events (AEs) after 16 treatment weeks.

Results: 43 Cobra Slim and 47 MTX-TSU patients were analyzed: 65.1% in the Cobra Slim group and 46.8% in the MTX-TSU group reached remission (p=0.081). Mean ± SD AUC-DAS28(CRP) was 13.84 ± 4.58 and 11.18 ± 4.25 for the MTX-TSU and Cobra Slim patients respectively (p=0.006). More Cobra Slim patients had a HAQ=0 (51.2% vs 23.4%, p=0.006) at week 16. Therapy related AEs did not differ.

Conclusion: In patients with low-risk eRA, MTX with step-down glucocorticoid bridging seems more efficacious than MTX step-up monotherapy with a comparable number of AEs over the first 16 treatment weeks.

Introduction:

Current guidelines recommend treating patients with early Rheumatoid Arthritis (eRA) immediately, intensively and to target [1-3]. Early intensive treatment strategies combining classical Disease Modifying Anti-Rheumatic Drugs (DMARDs) with rapid remission inducing agents like glucocorticoids (GCs) or biologicals are the most effective approach for eRA [4-6]. In daily practice, however, the initial treatment choice is based on physician's preference, patient and disease characteristics as well as cost issues [7]. Traditionally, the absence of bone erosions, Rheumatoid Factor (RF) or Anti-Citrullinated-Protein Antibodies (ACPA) and low disease activity are considered markers of a good prognosis, but the bad performance of these markers and derived matrices might lead to under treatment of so-called low-risk patients [8].

New very sensitive classification criteria for RA were developed in light of the early treatment paradigm [9], but patients with eRA still form a heterogeneous group [10]. Current treatment recommendations are mostly based on evidence from Randomized Controlled Trials (RCT) in preselected populations with a poor prognosis based on classical markers and high disease activity. Few studies examine how to treat patients not reflecting this classic RCT image of eRA.

Early intensive treatment appears successful also in undifferentiated arthritis, including patients with so-called pre-RA, but confirmation is needed in studies with a longer follow-up [11]. On the other hand some authors suggest that too stringent treatment targets might not outweigh potential side effects in eRA patients lacking poor prognosis markers [12].

This paper evaluates the efficacy and safety of step-up Methotrexate (MTX) with or without a step-down glucocorticoid bridging scheme after 16 weeks of treatment, in patients with eRA presenting without classical markers of poor prognosis.

Patients and methods:

This study is part of the Care in early RA (CareRA) trial, a Flemish prospective 2 year investigator-initiated multicenter RCT rooted in daily practice (EudraCTnumber: 2008-007225-39). The trial is conducted in 2 academic centers, 7 general hospitals and 4 private practices.

The ethics committee (EC) of the University Hospitals Leuven approved this study after consultation of the local ECs. All patients gave written informed consent. The full names of all approving ethical committees can be located within the Acknowledgements section

Patients

DMARD naïve patients with eRA, as defined by the American College of Rheumatology 1987 criteria, with a disease duration ≤1 year and aged ≥18 years, were recruited between January 2009 and May 2013. Patients having contra indications for MTX and/or GCs were excluded.

Eligible patients were stratified into a low or high-risk group. This allocation was based on classic RA prognostic factors: presence of erosions, presence of RF or ACPA and baseline disease activity score based on C-reactive protein [DAS28 (CRP)].

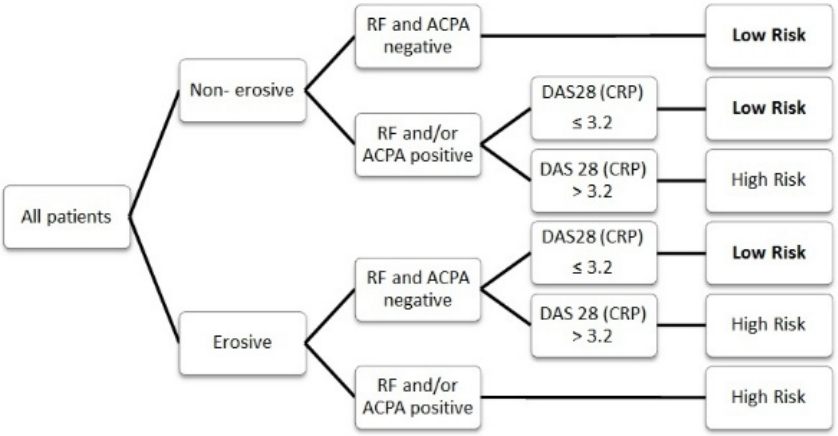
Patients were considered low-risk if:

- •No erosions + ACPA and RF negative
- •Erosions + ACPA and RF negative + DAS28 (CRP) ≤3.2
- •No erosions + ACPA/RF positive + DAS28 (CRP) ≤3.2

See figure 1 for more detail about the risk stratification.

Patients were assessed at screening, baseline, Week (W) 4, W8 and W16. If a treatment adjustment was required at W8, an optional visit was performed at W12. The analysis of the first 16 weeks in the high-risk arm of the CareRA trial was already reported in a separate paper [13].

Figure 1: Classification of patients in high or low risk according to classic prognostic factors



RF= Rheumatoid Factor, ACPA= Anti-citrullinated protein antibody, DAS28 (CRP) = 28 joint disease activity score calculated with C-reactive protein.

Design

Low-risk patients were randomized in 1 of 2 treatment arms:

- MTX Tight Step-Up (MTX-TSU): 15mg MTX weekly, no oral steroids allowed
- Cobra Slim: 15mg MTX weekly with a step-down scheme of daily oral GCs (30-20-12,5-10-7,5-5mg prednisone). From W28, GCs were tapered on a weekly basis by leaving out 1 daily dose each week over a period of 6 weeks, until complete discontinuation.

A treat-to-target approach was used in a tight-control setting [14], aiming for a DAS28 (CRP) ≤3.2 . If patients failed to reach this goal, treatment adjustments were made in both groups from W8: firstly a MTX dose-increase to 20mg weekly and secondly the addition of 10mg Leflunomide daily. Not reaching the target after these treatment adjustments was considered an efficacy failure. Intramuscular and intra-articular GC injections were allowed maximally every 8 weeks, except within 4 weeks preceding W16.

Outcome

The primary outcome was the proportion of patients in remission at W16, defined as a DAS28(CRP)<2.6. Secondary outcomes were the proportion of good EULAR responders, patients having a clinically meaningful Health Assessment Questionnaire (HAQ) response, patients having a HAQ=0 at W16 and cumulative disease activity.

Safety and toxicity

Patients were asked about experienced adverse events (AE) at each visit. Each reported AE was subtyped (toxicity, discomfort, infection, surgery or other) and evaluated for relation to the therapy, seriousness and severity by the treating rheumatologist. In case of toxicity, medication was adjusted according to a predefined scheme. Persistent toxicity was considered a safety failure.

Statistical analysis

No power calculation was done in view of the low-risk sub-analysis of the CareRA trial.

We performed an intention-to-treat (ITT) analysis by χ^2-test, Mann-Whitney-U test, Area-Under-the-Curve (AUC) and General-Estimated-Equations (GEE) analysis. Screening data were used to impute missing baseline data and vice versa. A maximum likelihood model was applied to impute missing data at W4, W8 and W16. Missing data at the optional visit W12 were imputed by taking the mean of W8 and W16. SPSS version 20.0 was used. A p-value < 0.05 was considered statistically significant.

Results

Ninety of the 380 patients in the CareRA trial were stratified as low-risk patients: 47 MTX-TSU and 43 Cobra Slim patients. Both groups had similar baseline characteristics, which reflect a mild eRA, with a moderate mean disease activity and low numbers of erosions, RF and ACPA positivity (table 1). One MTX-TSU and three Cobra Slim patients withdrew their consent before W16.

Table 1: Patients' characteristics at baseline per treatment group

	Tight Step Up	Cobra Slim
	n=47	n=43
Age (years)	51.02 ± 14.00	51.42 ± 14.42
BMI (kg/m²)	26.98 ± 4.22	25.40 ± 4.27
Gender (female)	80.9%	76.7%
Smoking Status (ever)	38.3%	48.2%
Alcohol Intake (yes)	61.7%	55.8%
Symptom Duration (weeks)	33.11 ± 62.21	34.42 ± 68.16
Comorbidities present (yes)	66.0%	60.5%
Morning Stiffness (yes)	68.1%	53.5%
RF (yes)	23.4%	25.6%
Anti-CCP (yes)	23.4%	27.9%
Erosions (yes)	0.0%	2.3%
Total TJC	14.06 ± 8.61	13.14 ± 10.70
Total SJC	10.00 ± 6.98	10.93 ± 7.55
PGA (0-100)	49.89 ± 22.99	48.60 ± 30.68
Pain (0-100)	52.09 ± 23.23	48.23 ± 31.19
Fatigue (0-100)	45.91 ± 22.07	39.40 ± 27.66
PhGA (0-100)	48.34 ± 23.37	48.63 ± 20.80
ESR (mm/h)	23.04 ± 16.90	30.00 ± 29.40
CRP (mg/l)	13.53 ± 18.62	20.14 ± 39.25
DAS28(ESR)	4.83 ± 1.68	4.88 ± 1.64
DAS28(CRP)	4.55 ± 1.63	4.50 ± 1.63
HAQ (0-3)	0.99 ± 0.67	0.92 ± 0.85

BMI= Body mass index; Alcohol Intake = consumption of any form of alcohol; Symptom duration = time elapsed between onset of symptoms and start of treatment; Disease duration = time elapsed between diagnosis of RA and start of treatment; Morning stiffness = being stiff in the morning for at least 45 minutes; RF= Rheumatoid factor; Anti CCP= Anti cyclic citrullinated protein; PGA= Patient global assessment; PhGA= Physician global assessment; TJC= Tender joint count; SJC= Swollen joint count; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28= 28 joint Disease activity score; HAQ= Health assessment questionnaire. Values reported are proportions or mean ± standard deviation.

Efficacy (table 2)

Primary and secondary outcomes

Remission was accomplished in 46.8% MTX-TSU and 65.1 % Cobra Slim patients (p =0.081). A good EULAR response was achieved in 44.7% of MTX-TSU and 58.1% Cobra Slim patients (p = 0.202). A clinically meaningful HAQ response was reached in 53.2% MTX-TSU and 62.8% Cobra Slim patients (p =0.357). Less patients had a HAQ=0 in the MTX-TSU (23.4%) compared to the Cobra Slim (51.2%) group (p=0.006).

Table 2: Clinical outcomes at week 16 per treatment group

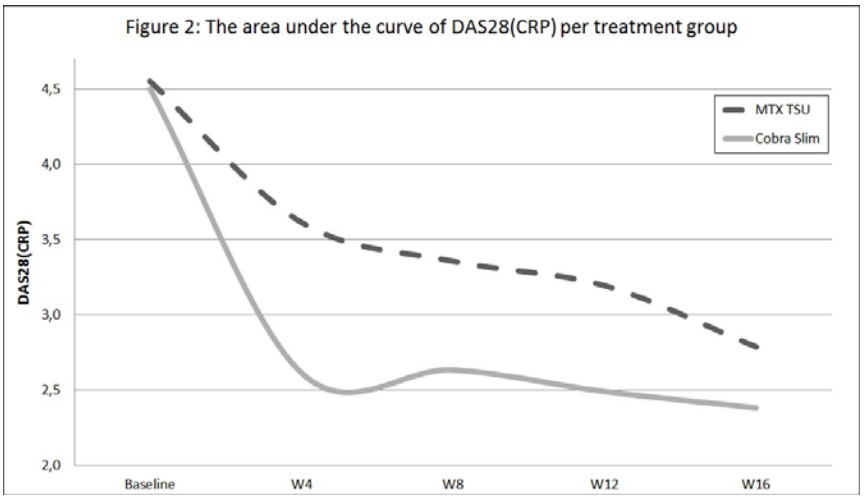
	Tight Step-Up	Cobra Slim	p-value
	n=47	n=43	
DAS28 (CRP) Change	1.76 ± 1.68	2.12 ± 1.41	0.192
Remission	46.8%	65.1%	0.081
Low Disease Activity	72.3%	79.1%	0.458
Good Eular Response	44.7%	58.1%	0.202
Moderate Eular Response	72.3%	86.0%	0.111
HAQ Change	0.40 ± 0.62	0.58 ± 0.64	0.267
Clinically Meaningful HAQ Change	53.2%	62.8%	0.357
HAQ is Zero	23.4%	51.2%	0.006

DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein; DAS28(CRP) change = DAS score on baseline minus DAS score on week 16; Remission is defined as DAS28(CRP) <2.6; Low Disease Activity is defined as DAS(CRP) ≤3.2; Good Eular Response is defined as low disease activity with a DAS28(CRP) change >1.2. Moderate Eular Response is defined as DAS28(CRP) change >1.2 or a DAS28(CRP) ≤5.1 and a DAS28(CRP) change between 0.6 and 1.2; HAQ = Health Assessment Questionnaire; HAQ change = Baseline HAQ minus week 16 HAQ; clinically meaningful HAQ change is defined as a HAQ change >0.22. Values reported are proportions or mean ± standard deviation. χ^2-tests and Mann-Whitney-U tests were applied when appropriate. The significance level was 0.05.

Longitudinal analyses

The mean ± SD AUC DAS28(CRP) was 13.84 ± 4.58 and 11.18 ± 4.25 for the MTX-TSU and Cobra Slim patients respectively (p=0.006)(Figure 2). GEE analysis showed a better treatment effect of Cobra Slim over MTX-TSU on longitudinal disease activity (p=0.005).

Figure 2: The area under the curve of DAS28(CRP) per treatment group



Treatment adaptations

At W8, treatment adjustments were performed in 34.0% of MTX-TSU patients and 23.3% of Cobra Slim patients (p=0.259). At W16, treatment adjustments were performed in 21.3% of MTX-TSU patients and 16.3% of Cobra Slim patients (p=0.545). One Cobra Slim patient was considered an efficacy failure at W16.

Intra-articular GC injections were given in 21.3% of MTX-TSU and 7.0% of Cobra Slim patients (p=0.054). Only one MTX-TSU patient received two GC injections.

Safety

Until W16, therapy related AEs were reported in 44.7% of MTX-TSU and in 39.5% of Cobra Slim patients (p=0.622). MTX-TSU was related to 32 and Cobra Slim to 30 AEs, with a similar distribution for discomfort and toxicity (table 3). In the MTX-TSU group 11/23 AEs related to discomfort were intestinal problems (nausea and diarrhea), while 10/23 discomfort problems in the Cobra Slim group were intestinal issues (nausea and constipation). In the Cobra Slim group, there were 2 cases of increased appetite. Furthermore, 8/23 discomfort problems in the MTX-TSU and 8/23 AEs related to discomfort in the Slim group were general malaise problems (dizziness, agitation, headache, fatigue). There were 7 toxicity problems related to therapy in the MTX-TSU group: 4 cases of abnormal liver values, 1 case of abnormal kidney values, 1 oral ulcer and 1 pyrosis. In the Cobra Slim group there were 4 toxicity problems related to therapy: 2 cases of alopecia, 1 tendinitis and 1 stomatitis. The only infection in our study was an upper respiratory tract infection in a MTX-TSU patient. No serious adverse events were registered. Mean ± SD Weight gain was 0.00 ± 2.44 kg in the MTX-TSU group and 0.70 ± 3.16 kg in the Cobra Slim group (p=0.287). Mean ± SD BMI gain was 0.01 ± 0.90 kg/m² in the MTX-TSU group and 0.23 ± 1.12 kg/m² in the Cobra Slim group (p=0.286).

Table 3: Number of adverse events per treatment group

		Tight Step Up	Cobra Slim
		n=47	n=43
AE related to therapy		32	30
Type related AE	Discomfort	23	23
	Toxicity	7	4
	Infection	1	0
	Others	1	3
	Surgery	0	0
Severity of related AE	Mild	29	28
	Moderate	3	2
	Severe	0	0
Serious AE		0	0

AE = Adverse event.
Protocol determines the severity rating of the adverse event:
-Mild (does not interfere with daily living)

-Moderate (somewhat interferes with daily living or medications needed to relieve event)
-Severe (incapacitating)

Discussion

We demonstrated that, although the primary outcome was not met at week 16, low-risk eRA patients treated with MTX and a step-down glucocorticoid bridging scheme showed a better cumulative control of disease activity over time and better functionality than patients treated with step-up MTX only, while having a similar safety profile during the first 16 treatment weeks.

In both groups favorable remission and low disease activity scores were achieved after 16 weeks. Efficacy scores didn't differ at W16, probably due to the limited number of patients included in this substudy, but also due to a trend for more treatment modifications and GC injections in the MTX-TSU group. The lower cumulative disease activity with Cobra slim during the first 16 weeks of treatment might have important consequences for the future disease course [15, 16]. Moreover, the speed of disease control and frequency in treatment adaptations could also have differential effects on the evolution of patient centered outcomes.

In this study, we applied a step-down bridge GC scheme which has two advantages over more traditional short-term low dosage GC use[17]. Firstly, high or moderately-dosed GCs demonstrate, apart from slow genomic effects, also faster non-genomic effects with a more profound impact on the disease process [18, 19]. Secondly, systematic and prolonged use of GCs is more efficacious than on demand use in the therapeutic time window before maximum DMARD efficacy [6, 20]. Intensive remission induction regimens appear to be equally advantageous in so-called low-risk as in high-risk eRA patients, but the appropriateness and performance of the currently used prognostic parameters need further evaluation in the long-term [8].

A significant finding is the safety profile of both groups. Patients in the MTX-TSU and Cobra slim group showed comparable numbers and types of adverse events related to therapy in the period their treatment schedules differed the most. Not much is known about the safety of short term glucocorticoid use. Our study adds to the much needed evidence about glucocorticoid use in the

management of early RA [21, 22] and shows that glucocorticoids are relatively safe to use in a remission induction scheme in patients with early RA, also in so-called mild RA. This result is in contrast to some rheumatologists' negative perception of glucocorticoid use in intensive treatment strategies in early RA [23], while patients themselves are rapidly convinced after glucocorticoid administration [24].

This explorative study has some limitations. Firstly, the total population in the low-risk arm is relatively small. Power calculation for the CareRA study was done in view of the high-risk subpopulation. Because 25% of patients were stratified as low risk patients, we did not achieve the same power as in the high risk arm. Therefore, results of our explorative study in the low risk arm should be interpreted with caution. Furthermore, the low number of low-risk patients is possibly responsible for the lack of statistical difference in the primary outcome at week 16. Secondly, we did not measure medication adherence and there was no blinding procedure, but this is unavoidable in a pragmatic trial reflecting daily clinical practice.
Thirdly, we report the results after 16 weeks of treatment, which is a relatively short time span to evaluate the full impact of a treatment strategy. This timing was chosen because there is increasing evidence that long term RA outcomes are mostly influenced by the initial success of treatment. Of course, the ultimate effect of treat to target adaptations according to the protocol cannot be evaluated in this time window.

Our exploratory data are of importance in the ongoing debate about the optimal initial treatment strategy for early RA in daily practice [25]. Patients with RA who are negative for biomarkers such as RF and especially ACPA are traditionally seen as having a better prognosis. Barra et al. have shown very clearly that this assumption is not always true [26]. The absence of serum markers for RA cannot be claimed to predict in general a milder disease course. This means that patients conventionally perceived as having a lower risk on a severe disease course should be treated according to the same standards as high-risk

patients. In this study we show that just like high-risk patients, so called low-risk patients can be more successfully treated with an intensive treatment strategy, while having a similar safety outcome as patients treated more conservatively. Until such time that prognostic factors can reliably stratify patients by prognosis to specific treatment approaches, our data suggest every RA patient could benefit from an upfront intensive treatment approach.

Conclusion

In conclusion, eRA patients, perceived to be at low-risk of a severe disease course, seem to improve more, at least in terms of cumulative disease activity and functionality, if treated intensively with MTX and a step-down bridge moderate-dose glucocorticoid scheme compared to with MTX alone over 16 weeks.

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Efficacy and safety of different remission induction strategies combining synthetic DMARDS with or without glucocorticoid bridging for early rheumatoid arthritis (CareRA): 1 year results of a randomized pragmatic superiority trial

Abstract

Background: Combining Disease Modifying Anti-Rheumatic Drugs (DMARDs) with glucocorticoids (GCs) is an effective treatment strategy for Early Rheumatoid Arthritis (ERA), yet the ideal schedule in daily practice is still a matter of discussion. Moreover, it remains unclear if treatment allocation has to differ depending on prognostic markers. In this study we aim to compare different DMARD combinations and GC remission induction schemes in poor prognosis patients and to evaluate Methotrexate (MTX) with or without GC remission induction in good prognosis patients, over a one year treatment period.

Methods: The Care in ERA (CareRA) trial is a 2-year investigator-initiated randomized pragmatic superiority trial, ran in 13 Flemish rheumatology practices. DMARD naïve ERA patients were stratified into a high- or low-risk group based upon presence of erosions, disease activity and serummarkers. High-risk patients were randomized to a Cobra-CLASSIC (MTX+Sulphasalazine+prednisone step-down from 60mg), Cobra-SLIM (MTX+prednisone step-down from 30mg) or Cobra-AVANT-GARDE (MTX+Leflunomide+prednisone step-down from 30mg) scheme. Low-risk patients were randomized to MTX with tight step-up (MTX-TSU) or Cobra-SLIM. The primary outcome was the proportion of patients in remission in both risk groups after 52 weeks in an intention-to-treat analysis.

Findings: 98 CLASSIC, 98 SLIM (high-risk), 93 AVANT-GARDE, 47 MTX-TSU and 43 SLIM (low-risk) were included. Remission was achieved in 64.3% (63/98) CLASSIC, 60.2% (59/98) SLIM (high-risk) and 62.4% (58/93) AVANT-GARDE patients at W52 (p=0.840); and in 57.4% (27/47) MTX-TSU and 67.4 % (29/43) SLIM (low-risk) patients (p=0.329). Less adverse events related to therapy occurred per patient in the SLIM (high-risk) compared to the CLASSIC or the AVANT-GARDE group (p=0.038). Adverse events were similar in MTX-TSU and SLIM (low-risk) patients (p=0.871).

Interpretation: GC remission induction with MTX shows similar efficacy as with DMARD combinations in poor prognosis ERA patients, regardless of the initial GC dose. In good prognosis patients, MTX with GC remission induction displays similar safety but an earlier disease control than without remission induction. Hence, MTX with a moderate GC dose remission induction scheme seems effective and safe for all ERA patients after 52 weeks.

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory condition, traditionally seen as a severe destructive joint disease associated with many comorbidities, putting a huge burden on both the affected individual as well as society. In the last two decades, the clinical prospects for RA patients have improved drastically thanks to extensive research identifying new treatment strategies and potent new drugs. Current international guidelines recommend to treat a patient with Early RA (ERA) early, intensively and to target (1-3).

These recommendations were prompted by trials using early intensive treatment strategies based on combinations of classical Disease Modifying Anti Rheumatic Drugs (DMARDs) and glucocorticoids (GCs) (4-10). These studies advocate the ‘‘window of opportunity” principle which states that if patients are treated intensively and early in the disease process and disease activity is rapidly controlled, they have definite benefit with better radiographic outcomes and preserved functionality later on. However, these strategies are not always implemented in daily clinical practice because of open questions regarding the optimal dosage and combination of drugs used. Indeed, Methotrexate (MTX) monotherapy might be sufficient to control ERA in many patients, and even in case of insufficient response, stepping-up to triple DMARD therapy or biological therapy could rescue them later on (11, 12). However, delaying optimal disease control unfortunately leaves some of these patients with unnecessary further suffering and loss of participation before arriving at endpoints targeted.

Guidelines also advise adapting treatment to the patient’s prognostic profile based on disease activity; and on the presence of erosions and/or autoantibodies (1-3). Such recommendations are mostly based on results from clinical trials in preselected populations and with a fixed treatment schedule without treating to target. The use of classical prognostic algorithms predicting structural damage proved to be unreliable in daily practice and scarce data suggest that patients with a better prognosis might be under-treated applying such principles (8, 13). To utilize the window of opportunity optimally, we hypothesize that a combination of classical DMARDs with rapid remission inducing agents like GCs or biologicals is the most effective approach for *all* patients with ERA emphasizing also the

need for further definition of the most feasible combination of drugs for daily practice.

GCs are commonly used to bridge the slow onset of classical synthetic DMARD effect. During the demanding early treatment period, GCs can relieve pain, stiffness and disability, allowing patients to promptly retake their place in society, and potentially preventing disease chronicity. Yet, the optimal initial dosage, treatment duration and administration route of GCs are up for discussion (14, 15). The role of GCs is still perceived as ambiguous, in both the patient's and the physician's mind (16, 17). Thus many rheumatologists hesitate to prescribe GCs due to fear for side effects and/or the confrontation with hesitation of their patients.

Biologicals combined with MTX are more efficacious than MTX monotherapy in ERA trials (18), but their temporary use as remission induction agents in bridging strategies just as GCs is less well studied. Most trial protocols led to persistent biological use after the early induction phase and only recently the feasibility of dose tapering has been shown. So far, TNF blocking agents didn't demonstrate superior efficacy compared to induction regimes with GCs (7, 19) and their cost-effectivity has not been demonstrated in ERA (20). The optimal and most feasible drug combination for ERA treatment is still up for debate. COBRA (Combination therapy for early Rheumatoid Arthritis)-like schemes (MTX± Sulphasalazine (SSZ) + GCs) Triple therapy (MTX, SSZ and Hydroxychloroquine (HCQ)), or other DMARD combinations demonstrate excellent clinical efficacy compared to monotherapy. However, studies comparing different combination regimens while following a treat to target approach are still scarce. Such studies are needed to inform the practicing physician.

The aim of the current study is to contribute in defining an optimal yet feasible therapy for every ERA patient. Therefore, we compare in patients with ERA the efficacy, effectiveness and safety of different initial DMARD combinations with or without GC bridging schemes, depending on the prognostic profile, 52 weeks after treatment initiation.

Methods

Study design

The CareRA trial (Care in early RA) is a 2 year prospective investigator-initiated multicenter pragmatic open-label randomized superiority trial. Thirteen Flemish rheumatology centers actively recruited: 2 academic centers, 7 general hospitals and 4 private practices.This study was approved by the central Ethics Committee (EC) of the University Hospitals Leuven and the local ECs. Detailed results of the first 16 treatment weeks, the crucial very early disease phase, were published elsewhere (21, 22).

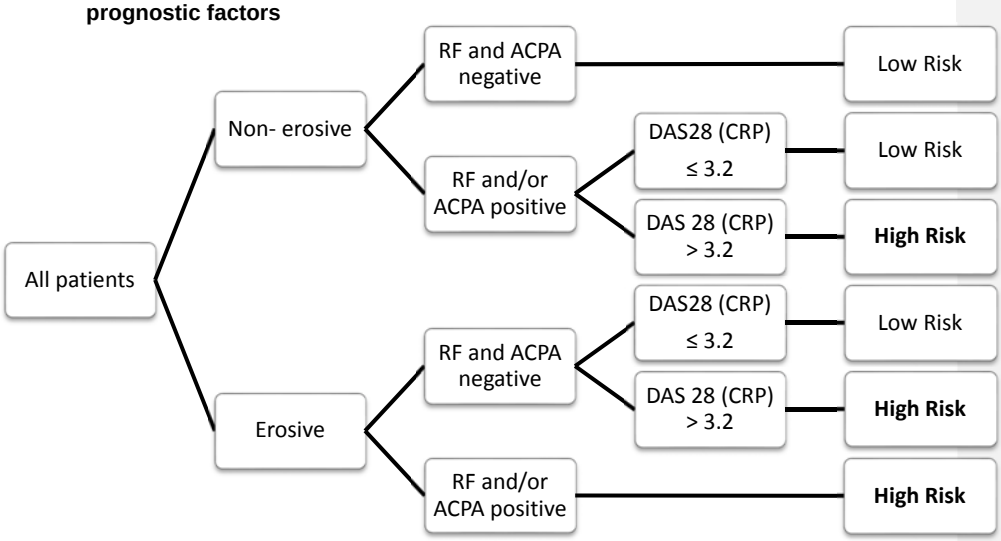
Patients

Patients with RA, as defined by the American College of Rheumatology (ACR) 1987 revised criteria, were recruited between January 2009 and May 2013. Main inclusion criteria were having a disease duration ≤1 year and being DMARD and GCs treatment naïve. Disease duration was time elapsed between RA diagnosis and treatment initiation. Patients having contra indications for intensive treatment combinations with GCs as judged by the treating rheumatologist were excluded. Supplement 1 gives a full list of exclusion criteria. Patients with specific co-morbidities such as controlled diabetes, osteoporosis and previous malignity were not excluded, reinforcing study generalizability. All patients gave written informed consent before inclusion.

Randomisation and Procedures

Patients were stratified to a high or low-risk group based on an algorithm constructed with classical RA prognostic factors: erosions, Rheumatoid Factor (RF) and/or anti-citrullinated protein antibody (ACPA) and disease activity score based on C-reactive protein (CRP) status [DAS28 (CRP)] at screening. (figure 1).

Figure 1: Classification of patients in high or low-risk according to classic prognostic factors



RF= Rheumatoid Factor, ACPA= Anti-citrullinated protein antibody, DAS28 (CRP) = 28 joint disease activity score calculated with C-reactive protein.

After risk allocation, high-risk patients were randomised via a computer sequence into 1/3 treatment arms:

- COBRA CLASSIC: 15mg MTX weekly, 2g SSZ daily and a weekly step-down scheme of oral GCs (60-40-25-20-15-10-7.5mg prednisone)
- COBRA SLIM: 15mg MTX weekly with a weekly step-down scheme of oral GCs (30-20-12.5-10-7.5-5mg prednisone).
- COBRA AVANT-GARDE: 15mg MTX weekly, 10mg Leflunomide (LEF) daily and a weekly step-down scheme of oral GCs (30-20-12.5-10-7.5-5mg prednisone).

Low-risk patients were randomised via a computer sequence into 1/2 treatment arms:

- COBRA SLIM
- MTX Tight Step-Up (MTX-TSU): 15mg MTX weekly, no oral steroids allowed.

No blinding procedures were undertaken in this pragmatic trial. Prophylactic treatment including oral folic acid, calcium and vitamin-D supplements was prescribed to all patients. Moreover, face-to-face education and standardized info-material (leaflet, DVD and website) was provided about the disease and the proposed treatment at screening. Additional information was given on demand.

The GC dose was tapered down weekly except for the lowest dose (7.5mg in COBRA CLASSIC and 5mg in the other arms), which was maintained until week (W)28. Then, GCs were further tapered on a weekly basis by leaving out 1 daily dose each week over a period of 6 weeks, until complete discontinuation at W34. MTX monotherapy at W40 was aimed for in all treatment arms, except in COBRA AVANT-GARDE. In this arm, patients were re-randomized at W40 to MTX or LEF monotherapy, if the disease activity was below 3.2 and in the absence of contraindications either for MTX or for Leflunomide..

Patients were treated to the target of DAS28(CRP) ≤3.2 in a tight control setting. If patients failed to reach this target, treatment adjustments were made according to protocol from week 8 onwards. The first adjustment in all treatment arms was an increase in the weekly MTX dose to 20mg. If necessary a second adjustment could be made from 8 weeks after the first adjustment. The second adjustment depended on the treatment arm: a SSZ dose increase to 3g daily in COBRA CLASSIC, the addition of 10mg LEF daily in COBRA SLIM and MTX-TSU or a LEF dose increase to 20mg daily in COBRA AVANT-GARDE. If patients did not reach the target after 2 predefined treatment adjustments, this was considered a strategy failure for efficacy reasons (efficacy failure). In case of toxicity, the protocol predefined schemes for tapering/interrupting the assigned treatment. If toxicity was persistent, this was considered a strategy failure for safety reasons (safety failure).
Intra-muscular/articular GC injections were allowed maximally every 8 weeks, but not within 4 weeks preceding W16 or W52. Concomitant therapy with NSAIDS and analgesics was allowed and registered.

Patients were assessed at screening, baseline, W4, W8, W16, W28, W40 and W52. Maximally four weeks were allowed between screening and baseline. In case treatment adjustment were required according to the protocol, optional visits could be performed at W12, W20, W24, W32, W36, W44 and/or W48. Demographics and clinical parameters (see table 1) were registered at screening and clinical evaluations, DAS28(CRP) and HAQ at every visit. X-Rays of hands and feet were obtained at baseline, W28 and W52. Patients experiencing efficacy or safety failures of the predefined treatment schedules were followed further and evaluated at W28 and W52.

Outcomes

The centrally assessed co-primary study endpoints were the proportion of patients in remission (DAS28(CRP)<2.6) at W52 –the subject of the present report-, at W16 already reported earlier (22) and at W104. Secondary efficacy outcomes were radiographic evolution by the Sharp Van der Heijde (SvdH) score, the proportion of good EULAR responders (DAS28(CRP) change>1.2 and DAS28(CRP)≤3.2), the proportion of patients having a clinically meaningful improvement of the HAQ (HAQ change>0.22) and the proportion of patients having a HAQ=0 at W52.

At each visit, patients were questioned about any adverse events (AE). Each reported AE was registered and evaluated in terms of relation to therapy, seriousness and severity by the treating rheumatologist. AEs were also divided in different subtypes: discomfort, toxicity, infection, surgery and a miscellaneous category. The categorization of all AEs was evaluated by the data monitoring team after 52 weeks and redefined where necessary to harmonize the safety data after approval of the individual investigators.

Statistical analysis

This study was designed as a superiority comparison of COBRA CLASSIC versus COBRA SLIM and COBRA AVANT-GARDE versus COBRA SLIM in the high-risk arm. Sample-size calculation was based upon the expected proportion of patients

in remission at W16 (22). Eighty-five patients per treatment arm were required for a power of 80% and significance level of 0.05, starting from an estimated clinically relevant difference in effect size of 20%. Analysis of the low-risk population was not powered, but was exploratory.

All patients were considered for analysis. Only patients who were incorrectly randomized or not fulfilling the in/exclusion criteria were omitted. Three databases were constructed to analyse this trial. The safety database registered the complete clinical data of all participants, even if patients were considered treatment or safety failures and were receiving medication deviating from the predefined protocol. This database was used for safety analysis. The per protocol (PP) database included only those patients who had followed the protocol strictly until the W52 endpoint. Hence, this database did not consider patients with efficacy or safety failures. This database was used for efficacy analysis. An intention-to-treat (ITT) database was constructed by imputing data when missing or from the moment they had to be disregarded because patients were considered efficacy or safety failures. This database was used for efficacy evaluation. The imputation of missing data was handled as follows. Screening variables were used to impute missing baseline variables and vice versa. To impute other data, the last observation carried forward method was applied.
Primary and secondary outcomes were examined by χ^2 or Kruskal-Wallis test, when appropriate. An ITT analysis was used to determine the primary outcomes. Radiographic images were scored via the SvdH method chronologically by 5 readers: one experienced reader (DDC) and 4 medicine students. An overlapping scoring scheme was constructed so that all images were scored by 2 students at least. The experienced reader scored all images. The mean score was retained in case of differences between readers. All statistical analyses were carried out using SPSS 22.0. A p-value <0.05 was considered statistically significant.

Results

In total, 400 patients were included in the CareRA trial between 1 January 2009 and 31 May 2013. The stratification resulted in 289 high-risk and 90 low-risk patients, 21 patients were excluded from analysis because of randomization errors or the discovery of exclusion criteria after randomization. Randomization was successful, resulting in similar characteristics in both risk groups (Table 1). Of the 289 high-risk patients, 98, 98 and 93 were randomized in the COBRA CLASSIC, SLIM and AVANT-GARDE arm respectively. Of the 90 low-risk patients, 47 and 43 were randomized in the MTX-TSU and COBRA SLIM group respectively.

Table 1: Patients' characteristics at baseline per treatment arm

	COBRA CLASSIC	COBRA SLIM (High-Risk)	COBRA AVANT-GARDE	MTX-TSU	COBRA SLIM (Low-Risk)
Number of patients	98	98	93	47	43
Age (years)	53.2 ± 11.9	51.8 ± 13.1	51.1 ± 12.8	51.0 ± 14.0	51.4 ± 14.4
BMI (kg/m²)	26.0 ± 4.3	26.8 ± 4.2	26.5 ± 4.2	27.0 ± 4.2	25.4 ± 4.3
Gender (female)	65.3%	64.3%	68.8%	80.9%	76.7%
Smoking Status (ever)	57.1%	59.2%	60.2%	38.3%	48.2%
Alcohol Intake (yes)	55.1%	56.1%	54.8%	61.7%	55.8%
Symptom Duration (weeks)	33.8 ± 35.5	33.2 ± 38.2	44.3 ± 65.9	33.1 ± 62.2	34.4 ± 68.2
Disease Duration (weeks)	1.8 ± 3.1	2.6 ± 3.3	3.1 ± 6.4	3.2 ± 6.6	1.9 ± 2.7
Employed before symptom onset (yes)	52.0%	65.3%	62.4%	66.0%	55.8%
Employed at screening(yes)	44.9%	53.1%	51.6%	57.4%	51.2%
Comorbidities at screening (yes)	72.4%	74.5%	65.6%	66.0%	60.5%
RF (yes)	79.6%	83.7%	75.3%	23.4%	25.6%
ACPA (yes)	77.6%	79.6%	77.4%	23.4%	27.9%
Erosions (yes)	32.7%	32.7%	34.4%	0.0%	2.3%
Total TJC	14.7 ± 9.5	13.7 ± 8.2	14.1 ± 9.0	14.1 ± 8.6	13.14 ± 10.70
Total SJC	11.9 ± 8.9	10.8 ± 6.5	10.6 ± 6.7	10.0 ± 7.0	10.9 ± 7.6
PGA (0-100)	59.5 ± 21.7	56.2 ± 21.7	54.8 ± 24.2	49.9 ± 23.0	48.6 ± 30.7
Pain (0-100)	59.5 ± 23.6	56.5 ± 21.9	57.5 ± 23.8	52.1 ± 23.2	48.2 ± 31.2
Fatigue (0-100)	50.6 ± 26.0	49.0 ± 21.3	48.9 ± 23.7	45.9 ± 22.1	39.4 ± 27.7
PhGA (0-100)	54.7 ± 18.5	53.1 ± 18.1	51.7 ± 17.9	48.3 ± 23.4	48.6 ± 20.8
ESR (mm/h)	33.5 ± 25.2	32.1 ± 23.4	25.0 ± 17.6	23.0 ± 16.9	30.0 ± 29.4
CRP (mg/l)	19.7 ± 28.9	21.5 ± 33.2	14.5 ± 19.2	13.5 ± 18.6	20.1 ± 39.3
DAS28(ESR)	5.4 ± 1.3	5.2 ± 1.2	5.0 ± 1.3	4.8 ± 1.7	4.9 ± 1.6
DAS28(CRP)	5.0. ± 1.2	4.8 ± 1.1	4.7 ± 1.2	4.6 ± 1.6	4.5 ± 1.6
HAQ (0-3)	1.2 ± 0.7	1.0 ± 0.7	1.0 ± 0.6	1.0 ± 0.7	0.9 ± 0.9

BMI= Body mass index; Alcohol Intake = consumption of any form of alcohol; Symptom duration = time elapsed between onset of symptoms and start of treatment; Disease duration = time elapsed between diagnosis of RA and start of treatment; RF= Rheumatoid factor; Anti CCP= Anti cyclic citrullinated protein; PGA= Patient global assessment; PhGA= Physician global assessment; TJC= Tender joint count; SJC= Swollen joint count; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28= 28 joint Disease activity score; HAQ= Health assessment questionnaire. Values reported are proportions or mean ± standard deviation.

Efficacy analysis

In the ITT analysis of the high-risk group, the primary outcome did not differ between groups. Remission was achieved in 64.3% (63/98) COBRA CLASSIC patients, 60.2% (59/98) COBRA SLIM patients and 62.4% (58/93) COBRA AVANT-GARDE patients (p=0.840) at W52. A good EULAR response was reached in 67.3% of CLASSIC patients, 68.4% of SLIM patients and 67.7% of AVANT-GARDE patients (p=0.995). A clinically meaningful HAQ response was reached in 68.4% of CLASSIC patients, 70.4% of SLIM patients and 71.7% of AVANT-GARDE patients (p=0.877). HAQ=0 was achieved in 37.8% of CLASSIC patients, 36.7% of SLIM patients and 44.1% of AVANT-GARDE patients (p =0.533).

In the ITT analysis of the low-risk group, remission was accomplished in 57.4% (27/47) MTX-TSU and 67.4 % (29/43) COBRA SLIM patients (p=0.329). A good EULAR response was achieved in 57.4% of MTX-TSU and 60.5% SLIM patients (p=0.771). A clinically meaningful HAQ response was reached in 57.4% MTX-TSU and 55.8% SLIM patients (p=0.876). HAQ=0 was accomplished in 29.8% of MTX-TSU and in 48.8% of SLIM patients (p=0.064).

PP analysis showed similar results (data not shown).

Table 2a: Clinical outcomes at week 52 per treatment arm in the high-risk group

	Cobra Classic	Cobra Slim (High-risk)	Cobra Avant-Garde	p-value
Number of patients	98	98	93	
DAS28 (CRP) Change	2.5 ± 1.5	2.3 ± 1.4	2.3 ± 1.5	0.329
Remission	64.3%	60.2%	62.4%	0.840
Low Disease Activity	74.5%	75.5%	79.6%	0.684
Good Eular Response	67.3%	68.4%	67.7%	0.995
Moderate Eular Response	84.7%	88.8%	88.2%	0.654
HAQ Change	0.7 ± 0.7	0.5 ± 0.7	0.6 ± 0.7	0.368
Clinically Meaningful HAQ Change	68.4%	70.4%	71.7%	0.877
HAQ = 0	37.8%	36.7%	44.1%	0.533

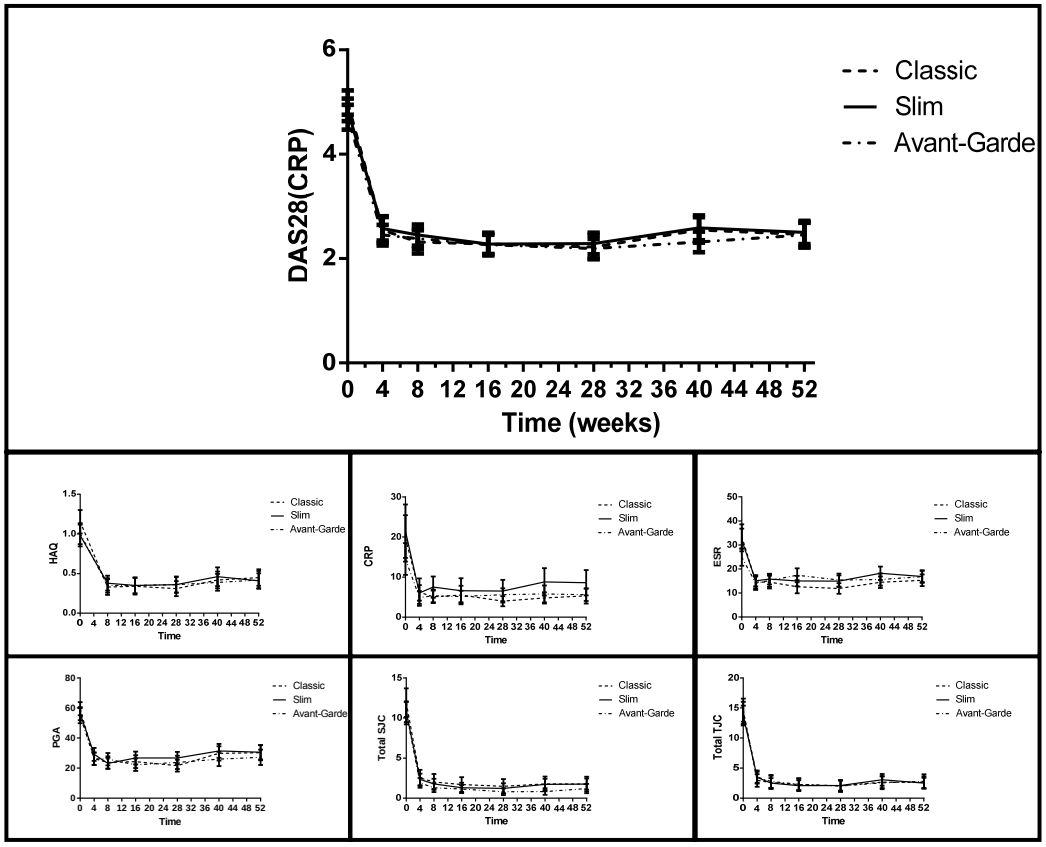
Table 2b: Clinical outcomes at week 52 per treatment arm in the low-risk group

	MTX-TSU	Cobra Slim (Low-risk)	p-value
Number of patients	47	43	
DAS28 (CRP) Change	2.1 ± 1.7	2.1 ± 1.9	0.990
Remission	57.4%	67.4%	0.329
Low Disease Activity	76.6%	81.4%	0.577
Good Eular Response	57.4%	60.5%	0.771
Moderate Eular Response	78.7%	76.7%	0.822
HAQ Change	0.5 ± 0.6	0.6 ± 0.7	0.832
Clinically Meaningful HAQ Change	57.4%	55.8%	0.876
HAQ = 0	29.8%	48.8%	0.064

DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein; DAS28(CRP) change = DAS score on baseline minus DAS score on week 52; Remission was defined as DAS28(CRP) <2.6; Low Disease Activity was defined as DAS(CRP) ≤3.2; Good Eular Response was defined as low disease activity with a DAS28(CRP) change >1.2. Moderate Eular Response was defined as DAS28(CRP) change >1.2 or a DAS28(CRP) ≤5.1 and a DAS28(CRP) change between 0.6 and 1.2; HAQ = Health Assessment Questionnaire; HAQ change = Baseline HAQ minus week 52 HAQ; clinically meaningful HAQ change was defined as a HAQ change >0.22. Data are presented as mean ± standard deviation or as percentages. Statistical analysis was performed by χ^2 or Kruskal-Wallis test. A p-value <0.05 was considered statistically significant.

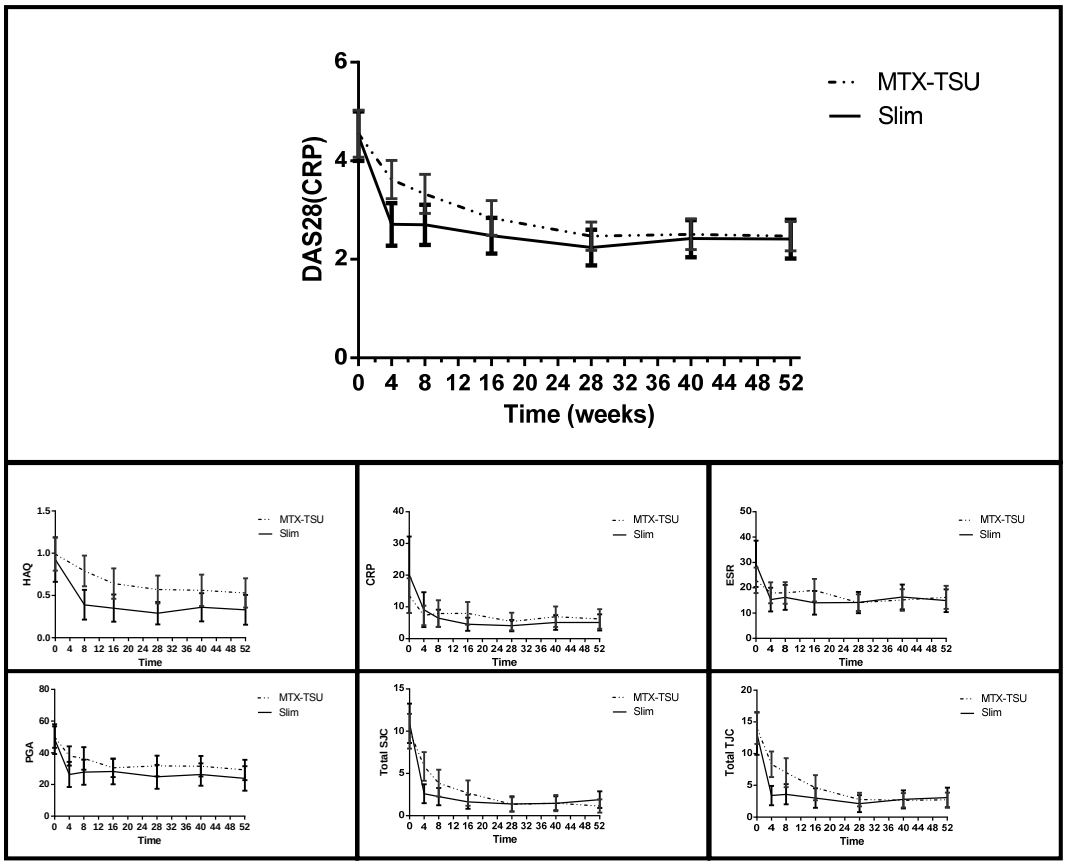
The mean ±SD AUC for DAS28(CRP) from baseline to W52 was 35.0 ±11.6, 35.3 ±10.6 and 33.9 ±8.6 for the CLASSIC, SLIM and AVANT-GARDE respectively (p=0.685). MTX-TSU patients had a higher AUC for DAS28(CRP) than Cobra Slim patients over 52 weeks of treatment in the low-risk group (42.0 ± 13.1 vs 35.8 ± 14.1, p=0.017). Figure 3a and 3b display the disease evolution from baseline until week 52 in the high and low-risk group.

Figure 3a. The disease evolution from baseline until week 52 in the high-risk group



DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein; HAQ = Health Assessment Questionnaire; CRP= C-reactive protein expressed in mg/l; ESR= Erythrocyte sedimentation rate in mm/hour. PGA = Patient Global Assessment on a visual analogue scale from 0-100; Total TJC= Total Tender Joint Counts; Total SJC= Total Swollen Joint Counts. Values reported are proportions or mean ± standard deviation.

Figure 3b. The disease evolution from baseline until week 52 in the low-risk group



DAS28(CRP) = 28 Joint disease activity score calculated with C-reactive protein; HAQ = Health Assessment Questionnaire; CRP= C-reactive protein expressed in mg/l; ESR= Erythrocyte sedimentation rate in mm/hour. PGA = Patient Global Assessment on a visual analogue scale from 0-100; Total TJC= Total Tender Joint Counts; Total SJC= Total Swollen Joint Counts. Values reported are proportions or mean ± standard deviation.

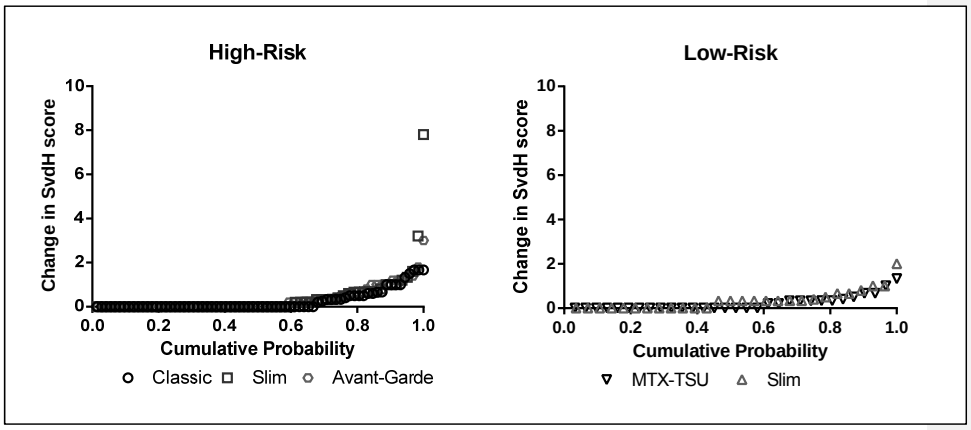
80% of baseline X-ray images of hands and feet were available. Overall, baseline structural damage and radiographic progression were minimal in all groups. Table 3 gives more insight in the radiographic evolution.

Table 3: Radiographic evolution per treatment arm from baseline until W52

	Total population	High-Risk				Low-Risk		
		COBRA CLASSIC	COBRA SLIM (High-Risk)	COBRA AVANT-GARDE	p-value	MTX-TSU	COBRA SLIM (Low-Risk)	p-value
Number of patients	N=379	N=98	N=98	N=93		N=47	N=43	
N	303	82	75	78		34	34	
SvdH score Baseline	1.1 ±1.9	1.3 ±2.1	1.3 ±2.5	1.0 ±1.5	0.895	0.7 ±1.1	0.9 ±1.5	0.536
N	306	80	76	79		37	34	
SvdH score W28	1.3 ±2.2	1.5 ±2.5	1.5 ±2.9	1.2 ±1.6	0.853	0.8 ±1.2	1.0 ±1.6	0.579
N	303	81	77	76		37	32	
SvdH score W52	1.4 ±2.4	1.7 ±2.7	1.7 ±3.3	1.3 ±1.8	0.901	0.9 ±1.3	1.2 ±1.8	0.228
N	272	73	67	71		31	30	
Change BL-W28	0.2 ±0.5	0.1 ±0.3	0.3 ±0.8	0.2 ±0.4	0.581	0.1 ±0.2	0.1 ±0.2	0.586
N	269	74	68	68		31	28	
Change Bl-W52	0.3 ±0.67	0.3 ±0.5	0.4 ±1.1	0.3 ±0.6	0.819	0.2 ±0.3	0.3 ±0.5	0.257
N	291	76	74	74		35	32	
Change W28-W52	0.1 ±0.4	0.1 ±0.3	0.2 ±0.5	0.2 ±0.4	0.856	0.1 ±0.2	0.2 ±0.5	0.376

N = number of available X rays. SvdH = Sharp van der Heijde score. Radiographic images were scored via the Sharp Van der Heijde (SvdH) score method. No imputation of missing data was done. Data is presented as mean ±standard deviation.

Figure 4: Cumulative Probability Plots of the radiographic progression of the High and Low-risk group



Each dot represents a patient.

Safety analysis

Safety analysis in the high-risk group showed that AEs were reported in 67.3%, 66.3% and 76.3% of CLASSIC, SLIM and AVANT-GARDE patients respectively (p=0.255). Per patient 1.8±2.0, 1.3±1.4 and 1.9±1.6 AEs occurred in the CLASSIC, SLIM and AVANT-GARDE group respectively (p=0.038). Two serious AEs were reported in each treatment arm. Most adverse events related to gastro-intestinal problems and a general unwell feeling. To be noted were the higher number of AES with intestinal troubles and diarrhea in the AVANT-GARDE group and the higher number of AEs with general malaise symptoms and appetite changes in CLASSIC patients.

In the low-risk group, the numbers of AEs were 48 in 27 MTX-TSU patients and 49 in 20 Cobra Slim patients (p=0.871). AEs were reported in 63.8%, and 51.2% of MTX-TSU and SLIM patients respectively (p=0.224). Per patient 1.2±1.2 and 1.2±1.4 AEs occurred in the MTX-TSU and SLIM group respectively (p=0.737). Remarkably, gastro-intestinal problems and a general unwell feeling, the two most frequent groups of AEs, were similar between groups. Only higher number of AEs related to increased appetite was noted in the SLIM group. Two serious AEs (pulmonary infection and anemia) were registered in the SLIM group and none in the MTX-TSU group.

Discussion

Overall in the CareRA study, the COBRA SLIM combination yielded excellent results in all ERA patients regardless of classical prognostic markers at least in a treat to target approach, with high remission rates. Regardless of the prednisone dose in the remission induction scheme, in patients with markers of poor prognosis, DMARD combinations were not seen superior to MTX only with a moderate dose prednisone remission induction scheme, the so-called Cobra SLIM regimen, after a treatment period of 52 weeks. Furthermore, the safety profile of the latter treatment strategy was more favorable. In patients lacking markers of poor prognosis, MTX with or without a moderate dose prednisone remission induction scheme yielded similar efficacy and remarkably also similar safety results. However, the speed of treatment response and the lower cumulative disease activity over 52 weeks were more favorable in the treatment strategy with a GC remission induction scheme.

In patients perceived as having a more severe ERA, our findings have two implications. Firstly, combinations of DMARDs seem not more effective on the group level than MTX alone, when used with a moderate or high-dose remission induction scheme. A subgroup of patients could benefit from initial combination therapy. This subgroup can unfortunately not yet be predefined. Therefore, Cobra SLIM seems the most pragmatic initial approach for all patients, avoiding unnecessary “collateral damage” in terms of toxicity and intolerance. Moreover, our results show that patients in need of a more intensive therapy can catch up very rapidly if a treat to target approach is strictly followed. Contrary to our findings, the tREACH trial demonstrated that triple DMARD combination therapy was more effective than MTX monotherapy in association with GCs, but in that study a rather low-dose short term GC bridging strategy was used (23). In our trial, the time lag before full DMARD efficacy was bridged with more highly dosed GCs, probably removing any variance between the effects of different DMARD schedules. Hence, less DMARDs were required over time, which could impact adverse events and patients’ treatment adherence. Secondly, a high GC dose was not more advantageous compared with a moderate dose, regardless of the

DMARD strategy used. This could benefit the implementation of COBRA SLIM strategies in daily clinical practice. Den Uyl et al described comparable findings comparing an attenuated version with the original COBRA regimen in patients with moderately active ERA (24). Unfortunately, this study lacked decisive evidence; MTX was suboptimally dosed in the classical COBRA scheme and cumulative glucocorticoid dosages were comparable in the two schemes.

In patients without poor prognosis markers, MTX with and MTX without a moderate GC remission induction scheme displayed a similar efficacy at the one year endpoint. As shown in other studies, treatment strategies applying tight control with a treat-to-target approach seem to have converging efficacy in time, although in our data a clear trend for a higher efficacy was notable in MTX with GC remission induction, certainly in terms of cumulative disease activity over the first year (25). Moreover, treatment response is almost immediate in MTX with GCs, which seems more in accordance with patients preferences (26). The most outstanding finding in this low-risk population was however the safety profile. Both arms showed comparable numbers and types of adverse events related to therapy. Our study adds to the much needed evidence about glucocorticoid use in the management of early RA and showed that, apart from being efficacious, glucocorticoids are relatively safe to use in a remission induction scheme also in patients with so-called mild RA.

A limitation is that medication adherence was not measured. However, if adherence was lower in a certain treatment arm, the same could be expected in daily clinical practice. Secondly, no blinding was implemented. These two limitations related to the trial design are unavoidable in a pragmatic trial aiming to reflect daily clinical practice.
For the interpretation of the results in the high-risk patients, representing 75% of our study population, a limitation is the superiority design of this study. Therefore, we were only capable to demonstrate non-superiority of Cobra Classic and Cobra Avant-Garde versus Cobra Slim and not equivalence. The remaining 25% of our population were stratified as low-risk patients. Hence, we could not achieve the

same power in this arm as in the high-risk arm. Therefore, these results should be interpreted as explorative and in need of confirmation.
Finally, remission based on the DAS28(CRP) criteria was chosen as endpoint by protocol. This remission criterion is less stringent than the recently developed criteria (27).

The major strength of our study is that it was designed to provide an optimal treatment solution for all patients with RA which is of relevance for decision making by rheumatologists facing ERA patients in daily practice. Most classical trials preselect or try to find subpopulations which are most responsive to the treatment strategy under investigation. However, correct and unbiased predicting of the treatment response is still impossible in most patients with RA, using classical markers of disease prognosis (13, 28, 29). Hence, patients conventionally perceived as having a lower risk of a severe disease course can now be treated according to the same standards as high-risk patients.

Despite the very high efficacy numbers in our trial, 20% of patients with ERA do not reach these target criteria as proposed by international guidelines. Future research should investigate reliable markers for optimal treatment steering and for timely identification of patient groups, susceptible to failure of standard treatment.

In conclusion, we propose an efficacious standardized treatment for all patients with RA: COBRA SLIM, methotrexate combined with a moderate dose GC remission induction scheme. This scheme seems as effective as DMARD combinations with GC remission induction, and shows excellent clinical efficacy results in a setting reflecting clinical practice. Furthermore, the safety profile of COBRA SLIM seems comparable with MTX monotherapy while the treatment response is more rapid, immediately relieving patients from pain and dysfunctionality.

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General discussion

In the previous chapters, we dealt with three crucial aspects of early Rheumatoid Arthritis (RA) management. Firstly, we investigated if patients were treated in time after symptom onset. Subsequently, we explored the value of classical prognostic biomarkers in daily clinical practice. Finally, we studied the optimal intensive treatment strategy in newly diagnosed patients with RA. In this general discussion we will address the same themes. Although a partial overlap is hard to avoid, we believe all three aims of this doctoral thesis warrant their own critical evaluation. The discussion of each of the three thematic parts of this thesis will always follow the same structure. Firstly, we discuss the importance and the novelty of our studies. Secondly, we debate the methodological considerations. Thirdly, we give suggestions for future research and clinical practice. To conclude, we discuss the overarching message of this thesis and the practical consequences for the treatment of a patient with RA in daily practice.

Timely treatment (Chapter 1)

What have we learned?

Our research quantified the time elapsed between symptom onset and treatment initiation in Flanders for the first time (1) enlarging the current efforts of other groups in the field (2-4). Herein, We demonstrated that only **a minority of newly diagnosed RA patients is seen in time**, within the apparently elusive 12 weeks after symptom onset. Patients with more severe disease characteristics at baseline seemed to present earlier to the rheumatologist. Moreover, we demonstrated **a difference in treatment delay between the different types of rheumatology practices**: patients treated in academic and general hospitals showed longer treatment delays than those treated in private practices. A reason for this difference could not be found in variations in the patient characteristics at baseline. Furthermore, according to our findings **patient-related delay contributed the most to overall treatment delay** in Flanders.

This research was extended in two subsequent studies from our group, enriching the obtained data. Firstly, we explored the influence of psychosocial variables on treatment delay (5). We hypothesized that demographic and clinical characteristics could never fully explain the individual differences in treatment

delay. A person's individual help-seeking behavior is unlikely to be only determined by these 'easy to measure' factors, but probably also by a complex system of cognitive and emotional pathways (6). We used the illness perceptions questionnaire and the Utrecht Coping List to give us an idea of an individual's motivation to seek help. Intuitively, these psychosocial instruments both seem strong predictors of health behavior in general (7). Although these instruments are both validated (8, 9), measuring such a multifaceted attitude towards a disease remains challenging (10, 11). Nevertheless, we demonstrated that **coping and illness perceptions did indeed have an influence on timely treatment**, and even in the same magnitude as clinical variables.

Secondly, we have investigated in more detail the patient-related delay and the help-seeking behavior before referral to a rheumatologist (12, 13). This quantitative assessment was evoked by our primary delay study showing that patient-related delay contributed the most to the overall treatment delay. Therefore we constructed a rudimentary assessment form assessing the first symptoms and the initial help-seeking trajectory; the reasons why persons were seeking help, which Healthcare Professional (HCP) they initially contacted, if this HCP recognized RA and how long it took to suspect RA, which steps the HCP undertook and to whom the persons were referred. Patients followed in the CareRA trial were guided through this assessment form by one of two study team members to increase reliability. The investigators recorded any relevant additional information provided by the patient as sketches and notes. The main findings of this side study were that **pain was the most prominent initial symptom and the primary reason to visit the HCP**. Furthermore, **a quarter of patients indicated that five visits or more were needed before RA was suspected by a HCP**. Another qualitative study by our research group revealed that many general practitioners (GP) had doubts in their detection skill for RA (14). They indicated the lack of specificity of the initial symptoms, the absence of effective detection tests and the low incidence of RA in general practice as main confounders. As initial symptoms apart from joint pain, patients indicated joint swelling, joint rigidity, fatigue, morning stiffness and loss of strength as reasons to seek help in our study. Hence, GPs confronted with such general and

unspecific vague symptoms, suspected broad disease categories such as other musculoskeletal disorders but also unspecified local inflammation and overuse of joints. A majority of patients indicated also that blood tests were performed rather than a full clinical examination when they presented themselves to the initial HCP. Blood tests to detect autoantibodies and inflammation markers such as elevated CRP or ESR levels probably are meant to reassure the professional in the detection of RA, although these tests are never conclusive. Moreover, a part of the patients indicated that they had to return more than five times to the HCP before RA was detected, underlining the idea that uncertainty of the GPs was a barrier in the detection of RA in Flanders.

Methodological considerations

An important remark is that most of the influencing factors for delay were only **measured at the moment of inclusion in CareRA**, when patients presented themselves at the rheumatology practice or even later when treatment was already initiated, and not at the moment when the delay occurred. Yet, little is known about the evolution of rheumatic symptoms from symptom onset. The reliability of those predictors can thus be questioned. Other researchers have studied delay retrospectively, asking patients to recapitulate the initial symptoms or at least the 'earlier' symptoms from the moment of first visit to a rheumatology practice (3, 15). However, such investigations introduce probably the most common limitation to delay research: **recall bias**. Patients are asked several months after symptom onset when and how the first symptoms arose. We have tried to counter this almost unavoidable bias in our research by asking the GP the same information, as a kind of double-check.

A second consideration about our research is that not only individuals like the person with early symptoms of RA, the GP or the rheumatologist influence the treatment delay, but also **the overarching healthcare system**. A study by Raza et al has shown differences in total treatment delay between countries, but also differences in the types of delay influenced by the specific role the various stakeholders are playing in patients' help-seeking behavior (3). These results could indicate differences in healthcare pathways between countries. For

example, in some countries it could be hard to get an appointment with a GP while in other countries the access to a rheumatologist is more problematic than in others. In our research, the role of the healthcare system could not be determined, because we lacked a comparator population with a different healthcare organization.

Directions for future research and clinical practice

How can we shorten treatment delay?

From these studies exploring treatment delay in Flanders, it is clear that timely treatment should be further investigated and stimulated. Different targets for improvement can be identified (16).

First of all, **public awareness of RA** should be improved. Rheumatism is still seen in the community as a disease affecting primarily old people. However, many rheumatic conditions affect also the younger population. The question is if major public campaigns will address the right target audience. The FAST (Face-Arms-Speech-Time) approach for strokes or the breast lump for breast cancer are hallmarks for successful campaigns to raise awareness in public (17, 18). However, the indistinct and very individual symptom patterns of persons with RA make it more challenging. Furthermore, campaigns could have the opposite effect. Patients having other disorders could flood the general or rheumatologist practice, making time to get an appointment longer and thus increasing treatment delay instead of bringing it down (19). Therefore, a careful approach is needed when trying to increase public awareness towards RA by mass campaigns.

A key role in the Belgian healthcare system seems to be played by the GP who probably sees the persons with developing RA symptoms more frequently than any other HCP. **Reliable** tools such as **detection checklists should be constructed** and distributed so that the GP can develop self confidence in his or her RA detection skills (20-22).

Moreover, the patient stories in our study made clear that a multitude of HCPs are involved in the detection and diagnosis of RA. Hence, **a swift and reliable triage by different HCPs** could be an opportunity (23, 24). Aside of GPs and

rheumatologists, orthopedic surgeons, physical therapist, nurses and pharmacists were frequently consulted. Hence, it is key that also other **HCPs are properly educated in RA symptom detection**. In the training curriculum of physicians in Flanders, education about RA is already improved by multiple courses in musculoskeletal disorders but also by expert patients, teaching students and doctors how to recognize the symptoms of early RA during an anamnesis and how to examine the joints of patients with early RA; and sharing their own stories. A possibility is to further standardize and update these courses to educate all physicians up to the same level and to give such courses to a more broad audience of HCPs. As a result, the knowledge and the skill to detect RA could be extended to a larger group of individuals that could all be consulted, formally and informally, by persons with developing rheumatic symptoms.

Furthermore, **the connection between primary care and the rheumatology practice** should be improved. Initiatives are already undertaken in different countries (20, 25-27). Early RA clinics are a prime example of such an initiative. The general principle of such organization structures is to give patients with inflammatory arthritis swift access to the rheumatologist or specialist nurses. Many variations of such clinics exist. Some GPs and rheumatologist collaborate closely, sometimes in the same building, on a target population, to improve triage. In other clinics, all patients can come in with rheumatic symptoms and a triage system is set up to quickly find susceptible patients. Moreover, other methods are used such as keeping dedicated consultation slots for patients with early rheumatic symptoms at the rheumatology practice or a system of standard referral pathways.

How early is (too) early?

A second important question to address is when to treat. Nowadays, it is clear that individuals with a new diagnosis of RA should be treated as soon as possible. Hypothetically, treating patients with rheumatic complaints from the time of symptom onset would even be better. **Possibly, RA as a disease could be prevented this way** (4). However, the risk of overtreatment and stimulating the

development of unnecessary disease behavior is of course huge. The majority of patients with undifferentiated arthritis, possibly a precursor of RA, will not develop RA, although these patients often show the same initial indistinct symptom patterns as patients developing RA. The challenge for the future will be to find new and reliable markers for RA detection and testing these in cohorts of patients with RA-like complaints (28, 29), hence pushing the boundaries for optimal treatment initiation backward while not over treating the majority of patients.

Capturing the patient perspective

Our research has shown some indications that delay is not only driven by clinical symptoms but also by how persons cope when being confronted with the first signals of a rheumatic disease (5). HCPs should take such **personal traits into account when giving medical advice** to individuals with joint complaints or other more subtle signs and symptoms potentially related to developing RA. Unfortunately, research into this subject is lacking (4).

Classical Biomarkers of disease progression (chapter 2)

What have we learned?

We evaluated the predictive capacity of composite algorithms using classical prognostic markers to predict structural damage in patients with early RA (Chapter 4). We concluded that **none of these predictive matrices could be reliably used in daily clinical RA practice** (30). The results were unsatisfactory, although these matrices were constructed with widely used classical prognostic markers of RA, all of which were shown to have some association with structural damage individually. Yet, none of the patients developing rapid radiological progression in our cohort could be correctly identified. Moreover, these patients were even considered to be at low risk of structural progression according to the evaluated matrices. These findings were confirmed in a similar trial (31).

The 2010 EULAR guidelines for RA management suggested that patients without poor prognosis markers (absence of erosions, autoantibodies or high disease activity) at treatment initiation were not in need for a more intensive therapy approach (32). This category of patients was considered to respond equally well

to initial monotherapy as to intensive therapies. On the contrary, patients with a poor prognosis would benefit more from initial combination therapy. However, the new 2013 EULAR guidelines revoked these recommendations: every patient should receive the same treatment regardless of his/her risk profile (33). Paradoxically, the updated guidelines still recommend risk evaluation as an important aspect in the therapeutic approach of RA. Moreover, it is stated that the follow-up treatment of patients without poor prognosis markers should be different to patients with a poor prognosis after failure of initial MTX monotherapy. A post-hoc analysis of the BeSt study indicated that the rationale behind this statement should be reevaluated (34). Herein, it is suggested that tailored treatment is not yet feasible despite the current guidelines. Rapid relief of symptoms should be more the focus of treatment than prognostic factors. We explored the value of prognostic factors further in chapter 2. Herein we demonstrated that **an intensive approach with classical DMARD combinations and a GC bridging scheme seemed to be more effective than DMARD monotherapy** in achieving higher remission rates and less radiographic progression in a Belgian monocentric cohort after two years of treatment in daily clinical practice, **although patients were selected by the treating physician to receive a more conservative therapy if the RA profile of the patient seemed less severe at baseline** (35). In a tight control setting, rapid radiological progression (RRP) was inhibited in the majority of patients. Numerically, RRP occurred more in patients treated conservatively, although these patients had less severe RA characteristics.

Methodological considerations

These two studies made use of the same small monocentric observational cohort. No trustworthy causality could be shown because of the less controlled cohort setting and patient heterogeneity. For instance, the absence of a medication protocol and different baseline characteristics between the two group biases therapy comparison. Moreover, given the low numbers of RRP, chances that matrices would detect patients prone for structural damage are probably lower. Furthermore, RRP seems to be largely prevented by a treat to target strategy in a tight control setting. Therefore, from our point of view, the importance of X-ray damage as disease outcome parameter has become less important (31).

Directions for future research and clinical practice

The everlasting quest for a better RA biomarker

Many attempts have been made in RA research over the last decades to discover biomarkers capable of tailoring the right treatment to the right patient, especially on the genetic front (36). This thesis will not go to deep into this topic, but researchers should continue investigating biomarkers, because better markers will of course improve algorithms to predict RA outcomes such as structural damage or persistent inflammation. And although this might seem challenging, they should be tested in daily practice, in RA populations treated to target as required by the guidelines, and not in classical RCTs.

Initial treatment response as prognosis marker

Our studies have shown that the (combination of) current classical prognostic markers are not reliable enough to allocate patients to certain less or more intensive treatments in clinical daily practice. Recently, an interesting debate was initiated on ACPA status as predictive marker (37-40). ACPA negative patients seem to present with a more severe disease, but ultimately seem to evolve more beneficially (41). Such evidence is of course important to take into account when trying to find prognostic markers. It is not because a patient has a certain disease characteristic that make the disease look more or less severe at baseline, that the disease evolution should be neglected as a prognostic parameter. **Treatment response is a powerful predictive treatment marker in itself**, as demonstrated by different studies (42, 43). Unfortunately, treatment response is not something that can quickly be incorporated in predictive matrices at baseline. Perhaps a standardized treatment strategy with a swift treatment response can tackle such treatment allocation problems by quickly selecting patients with a good response, while not leaving the bad responders struggle for a long time. Hence, a predictive algorithm for bad responders after just a few weeks would be an ideal replacement for the matrices based exclusively on baseline parameters, which are at this point not reliable enough in daily practice.

Treating to target in daily clinical practice

Steering intensive therapy according to predefined targets, such as the DAS score, has been shown to yield better outcomes than routine care leaving treatment to the discretion of the physician (44). Furthermore, treating to target seems feasible in daily practice (45). However, we must realize that patient characteristics and preferences are considered by treating physicians to tailor treatment in real life (46, 47). Although clinical decisions based on gut feeling and experience are not always backed up by clinical evidence, they should not be pushed lightly aside as not being part of good clinical practice (48, 49). Future studies should **investigate the consequences of such a flexible treat to target** in which rheumatologists sometimes override the treat to target procedure because of -perceived - issues with safety, efficacy and patient preferences.

Optimal treatment strategy for a patient with early RA (chapter 3)

What have we learned?

The most effective current treatment options for the management of early RA are (combinations of) synthetic classic DMARDs with remission inducing agents such as GCs or biologicals in a tightly controlled treat to target setting (50). Chapter 3 firstly demonstrated that **DMARD combinations with a high or moderate dose GC remission induction scheme are not superior to MTX only with a moderate dose GC remission induction scheme in patients with poor prognosis markers** after 16 weeks of treatment in the CareRA trial (51). Efficacy of the three compared treatment strategies was similar. Yet, the safety profile was more advantageous for MTX only with a moderate GC scheme. Furthermore, chapter 3 showed that **MTX monotherapy with a moderate dose GC remission induction scheme seems more efficacious than MTX monotherapy without GCs in patients presenting without poor prognosis markers** after 16 weeks of treatment in the CareRA trial (52). Longitudinal analysis showed that disease activity and functional problems were lower in patients with a GC remission induction scheme. Most remarkable was the comparable safety profile between both treatments.

Lastly, chapter 3 investigated the efficacy and safety in the CareRA trial after 1 year of treatment for patients both with, and without poor prognosis. The results confirmed the findings at week 16. Hence, the general conclusion is that **MTX with a moderate dose glucocorticoid remission induction scheme - ''Cobra Slim'' - fits all patients with RA, with a high efficacy and acceptable safety profile.** This conclusion reinforces the idea that current prognostic markers intended to facilitate individual treatment decisions are overpowered by these intensive treatment strategies.

Methodological considerations

In the CareRA trial, **medication adherence was not measured** and **no blinding procedures were implemented**. This trial was set up to reflect daily clinical practice. If adherence was lower in a certain trial arm, the same could be expected from this treatment regimen in daily clinical practice. However, we cannot exclude that rheumatologists would still favor a particular strategy or patients would be more motivated for a specific regimen, influencing the results.

This trial was conceived as a superiority trial in patients with poor prognosis markers. Hence, we demonstrated **non-superiority** of DMARD combinations with GC remission induction schemes over MTX only with a GC remission induction scheme, which is not the same as claiming non-inferiority. Additionally, the sample of **patients presenting without poor prognosis markers was relatively small**. Hence, these results are explorative and in need for confirmation.

The **primary study endpoint** was the proportion of patients in DAS28 (CRP) remission defined by a cutoff of 2,6. Nowadays, remission criteria based on CDAI/SDAI and the more stringent ACR Boolean criteria have been proposed (53). The use of stricter remission criteria as targets for treatment is supposed to lead to a more long-standing disease control. Hence, theoretically, it could be advocated to investigate if a trial with a similar design as CareRA, but steered by other more stringent treat to target criteria, would show different results.

Directions for future research and clinical practice

The puzzle of glucocorticoids use

The role of GCs in RA therapy is disputed since their 'discovery' in the fifties. There are ardent supporters but also fierce opponents. However, the use of GCs is widespread in the rheumatologic community.

First of all, the starting dose of glucocorticoids is a matter of debate. GCs have their effects in a dose dependent manner (54). **Higher GC dosages** by higher saturation rates of the GC receptor **seem to induce more genomic transcription and fast non-genomic effects leading to more rapid inhibition of inflammation** compared to low GC dosages (typically lower than 7,5mg prednisone equivalents). Hypothetically, these added effects could explain the high efficacy of COBRA like schedules as demonstrated in the CareRA trial. However, higher dosages hold also the risk of more side effects (55). **The ideal glucocorticoid dose in terms of risk/benefit ratio is not yet clear**. In the CareRA trial we demonstrated that induction regimens with an initial prednisone dose of 30 mg daily were not less effective than the original COBRA schedule starting from 60 mg. However, It is questionable if a quest for a further dose reduction is worth the effort since moderate GC dosages (>10 mg of prednisone) are only used for a 3 weeks in these induction regimens. Moreover, we also showed in this trial that MTX with 30mg of prednisone initially versus MTX with no GCs yielded a similar safety profile, after 16 and 52 weeks of treatment. It could be debated that patients on GC therapy report less side effects because they experience less disease activity and feel thus more comfortable, but this could of course rather be seen as an advantage of therapy with GCs.

A second factor with **more importance than the exact dosage per day is the cumulative exposure to glucocorticoids over time**. In the CareRA trial, GCs are quickly tapered to a low dose and stopped after 6 months of treatment. Other trials use GCs, starting from low dosages, but use them much longer, for a year or two years. Hence, the cumulative dosage in these studies is much higher than in our trial. Therefore, we argue that not the starting dose, but the total cumulative dose should be the main focus in future trials. A very interesting trial design to prove our point in terms of GC dosing would be to compare MTX with a moderate

GC dose bridging scheme versus MTX with a low GC dose without tapering in the first year. Another issue is **the lack of a systematic standardized approach towards GCs**. Cobra like schedules are not frequently encountered in common practice, yet many different kinds of bridging schemes seem to be used by rheumatologists (56). Moreover, a majority of patients seem to be on some sort of GC therapy at most times in their treatment, although probably on low dosages (57, 58). This 'ad libitum' use seems perhaps innocent, but can lead to high exposure in the long term for many patients, explaining partly the perception of GCs as a medical product with many safety issues. This problem could explain possibly the reluctance by rheumatologists and other HCPs to implement Cobra like schedules with high starting dosages (47, 56). However, it seems that patients alter their perception on temporal GCs use when they experience the potent effect on pain and inflammation, regardless of the dose administered(59, 60). Hence, efforts should be made to standardize the use of GCs to increase its efficacy but at the same time diminish safety issues in the long run.

To combine or not to combine DMARDs?

Although we cannot predict individual response to treatment as shown in previous parts of the discussion, **some patients will probably benefit from initial DMARD combination** (39, 61, 62). Hence, physicians can still opt for **DMARD combinations, possibly with a slightly higher efficacy rate, but probably in exchange for more adverse events** (61). Furthermore, it is possible that DMARD combinations give better long term outcomes which should be evaluated in the longer run of the CareRA trial or possibly other similar trials.

Another interesting trial design would be a comparison between a COBRA like strategy and the popular triple therapy using MTX, SSZ and HCQ. The tReach trial already used a similar design comparing triple therapy with MTX only, both with a low dose GC bridging scheme for 10 weeks. Triple DMARDs was shown to be more efficacious than MTX only (62). The question is however if the GC bridging scheme in this trial was powerful enough to bridge the delay until maximum MTX efficacy. Ten weeks could be too short considering the fact that MTX maximum efficacy is often only reached after 3-4 months. However, the

results of this trial still indicate that some patients will probably benefit more from DMARD combination compared to MTX only.

Present and Future

This doctoral thesis gives indications as to how **a patient with newly diagnosed Rheumatoid Arthritis can achieve an excellent chance on a good disease outcome.** First of all, the patient must be detected, referred and treated as soon as possible. This initial treatment must be an intensive treatment that should be based on MTX with a remission induction scheme of glucocorticoids regardless of the patient profile, as determined by current classical prognostic markers. Furthermore, the patient should be followed in a tightly controlled setting, with swift treatment adaptations if the disease is not controlled sufficiently.

However, this thesis also shows there is still much to explore in future rheumatologic research. **The greatest challenges lays in defining RA as a disease entity and in predicting the course of this disease.** Both issues are reflected in the concept of tailored treatment. This concept is the grail of modern medicine, whereby any patient with a specific set of characteristics receives the ideal treatment for his or her disorder (63). Although much progress is made, tailored treatment in RA is still in its infancy. The first challenge is **what RA as a formal disease entity really encloses.** In many aspects we can see differences between patients with the same disease called RA: in terms of disease onset being it slowly or acute; periodically or gradually, in terms of clinical presentation and clinical response, but also not in the least in terms of in genetic background. Still, RA is regarded as a unique syndrome and consequently all RA patients are managed the same way. Hopefully, enough progress will be made in the future to increase the sensitivity and specificity of disease markers and clinical pattern recognition, making differentiation between RA subtypes possible.

The second challenge is the **lack of standardization in treatment**, initially, but especially during follow up. Physicians treat patients with different characteristics in various ways, based on clinical experience and scientific evidence. This differentiation based on gut feeling seems to work rather well, but strong evidence

for optimal treatment prediction is lacking. Most standardization is found in the early RA course. The guidelines now propose to use MTX as standard DMARD, sometimes associated with GCs (33, 64). Many studies propose schedules based on these recommendations (51, 52, 62, 65-71). These trials attain high proportions of patients in remission and low disease activity. However, an important proportion of patients still escape.

A third challenge is to explore why certain patients do not respond the same way on treatment as their counterparts. **A different genetic background or specific clinical and serological characteristics are classic culprits, but atypical causes such as treatment adherence or even the psychosocial profile of patients also deserve attention in future investigations** (72). Of course, combinations of these aspects are possibly more explanatory.

A fourth challenge is to standardize treatment after treatment failure. Patients initially doing fine on treatment, can fail later on in their disease course. This refractory RA is probably the main playfield for biological therapy. However, it is not yet clear what type of biologicals should be selected for which patients. In contrast, evidence exists that classical DMARD combination therapy can rescue many patients even in established disease (73). Additionally, new treatment targets and drugs are still being developed and refined. A new drug concept, the JAK inhibitors, can possibly add to a tailored treatment, but the role of these agents in RA management is still to be determined (74). **Algorithms defining treatment strategies later on in the disease course are lacking despite being important for the future of RA management.**

A fifth challenge is the **potential of tapering or even stopping therapies in patients with controlled disease** (75-77). Such strategies are very important also from the patient perspective (78). Drug free remission is an underexplored theme in RA, but will get more and more important when treatments become more efficacious at repressing the disease for long times.

To conclude, the treatment of RA changed drastically in the last decades. New treatment options, but especially improved treatment strategies changed the

classical image of RA patients from crippled invalids with joint deformities to self-confident individuals without external traits of their disease. This thesis explored further the optimal initial treatment strategies for patients with RA. Firstly, time is key in treatment of RA and the delay was found to be still too long in a majority of patients. Secondly, current classical biomarkers are not reliable in daily practice to tailor treatment to an individual patient. Thirdly, MTX only combined remission induction with a moderate dose of GC is a powerful and feasible option for all patients with RA. Future research should focus on improving the prediction of the disease course while not forgetting treatment feasibility in daily clinical practice and the patient perspective. The future looks bright for patients with RA!

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Addendum

CareRA: a 2 year prospective multicentre randomised controlled trial comparing effectiveness in daily practice of different treatment strategies for early RA

Investigators

This multicenter study is organised by the Department of Rheumatology of the University Hospitals Leuven in close collaboration with participating peripheral rheumatology practices. It will be coordinated by Patrick Verschueren together with René Westhovens.

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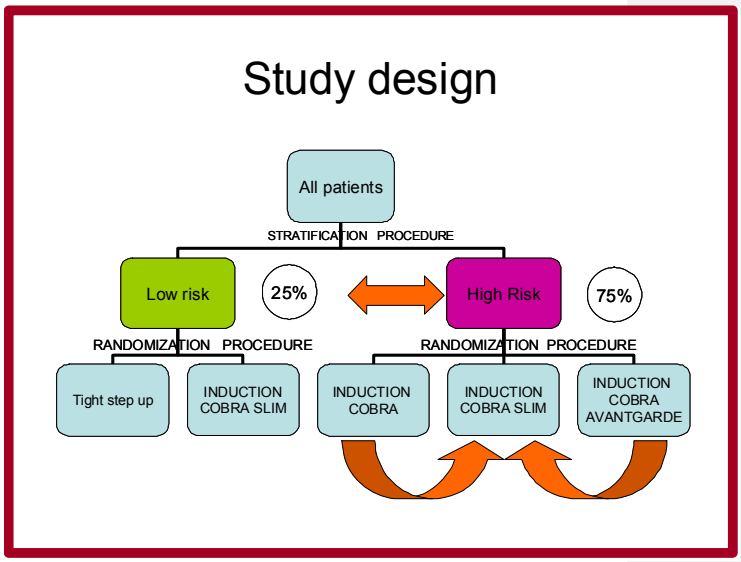
PROTOCOL SYNOPSIS CareRA

Title of the protocol	A two year prospective, multicentre, randomized, controlled trial comparing effectiveness in daily practice of different treatment strategies for early RA.
Study Population and enrolment period	A total of 400 patients are planned to be included in this study. This study has a duration of maximally 108 weeks (104 weeks of treatment and a maximal interval of 4 weeks between screening and baseline (w0)). The enrolment period is open from 2008 – 06/2013. Patients with severe RA will be randomly assigned to 1 of 3 treatment groups of 100 patients each according to a 1:1:1 ratio. Patients with less severe RA will be randomly assigned to 1 of 2 treatment groups of 50 patients each according to a 1:1 ratio.
Inclusion criteria	- Age ≥ 18 years - Diagnosis of RA as defined by the 1987-revised ACR classification criteria or the new ACR/Eular 2010 criteria for early RA - Early RA defined by a disease duration of ≤ 1 year - Use of a reliable method of contraception for women of childbearing potential - Able and willing to give written informed consent and participate in the study
Exclusion criteria	- Previous treatment with: o MTX or leflunomide o Cyclophosfamide, azathioprine or cyclosporine o SSZ for more than 3 weeks o Hydroxychloroquine for more than 6 weeks o Oral corticosteroids at a daily dosage of more than 10 mg prednisone equivalent within 4 weeks before baseline o Oral corticosteroids at a daily dosage equal to or less than 10 mg prednisone equivalent within 2 weeks before baseline o Oral corticosteroids for more than 4 weeks within 4 months before screening o Intra-articular corticosteroids within 4 weeks before baseline o An investigational drug for the treatment/prevention of RA. - Contra indications for corticosteroids - Contra indications for MTX, SSZ or Leflunomide o Known chronic hepatic disease (alcoholic, fibrosis, …) o Known pulmonary interstitial disease or fibrosis o Known chronic renal failure o History of malignant neoplasm within 5 years o Hematologic problems at the discretion of the investigator. - Psoriatic arthritis - Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study. - Pregnancy, breastfeeding or no use of a reliable method of contraception - Alcohol or drug abuse.

Study design	In this prospective, multicentre, randomized, controlled trial of 2-year duration, 400 patients with early active RA (≤ 1 year), previously untreated with DMARDs; will be stratified according to their disease severity and subsequently randomly assigned to different treatment strategies (see flow chart). Disease severity will be determined according to a scheme based on the presence of Rheumatoid Factor, anti-CCP antibody, erosions and disease activity.  **<u>Treatment regimens in the induction phase (Year 1)</u>** - **Tight Step Up:** MTX 15 mg and no additional oral steroids allowed - **COBRA classic:** MTX 15 mg with SSZ 2g and a step down scheme of steroids (60-40-25-20-15-10-7,5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and than tapered over 6 weeks). At week 40, patients will continue MTX (min. 15 mg/week) in mono therapy if disease activity is acceptable low (DAS 28 CRP ≤ 3,2) - **COBRA slim:** MTX 15 mg with a step down scheme of steroids (30-20-12,5-10-7,5-5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and than tapered over 6 weeks). - **COBRA avant-garde:** MTX 15 mg with Leflunomide 10 mg and a step down scheme of steroids (30-20-12,5-10-7,5-5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and than tapered over 6 weeks). At week 40, patients will be randomly assigned to maintenance therapy with either MTX (≥15 mg/week) or leflunomide (20 mg daily) if disease activity is acceptable low (DAS 28 CRP ≤ 3,2). **<u>Treatment regimen in the maintenance phase (Year 2)</u>**

	Treatment adjustments during the maintenance phase from w52 onwards will be at the discretion of the local physician according to good clinical practice.
Treatment adjustments during study	If patients fail to respond (DAS 28 CRP > 3,2), treatment adjustments will be made from 8 weeks of treatment onwards, if desirable and feasible. - First step: MTX dose increase to 20 mg per week in all groups - Second step: o COBRA classic: SSZ dose increase to 3 g o COBRA slim and Tight Step Up: add Leflunomide 10 mg o COBRA avant-garde: Leflunomide dose increase to 20 mg - An intramuscular depot-corticoid injection is allowed together with these treatment adjustments, but not within 4 weeks preceding week 16, 28, 40 and week 52 visits. As an alternative an oral bridging scheme could be considered, after discussion with the principal investigator. - Intra-articular corticosteroids are allowed maximally once every 8 weeks but not within 4 weeks preceding week 16, 28, 40 and week 52 visits - Further DMARD treatment adjustments are only allowed from 8 weeks after prior treatment adjustments onwards. If patients fail to respond (DAS 28 CRP > 3,2) after 2 treatment adjustments, from week 24 onwards = **treatment failures → treatment of choice = anti-TNF + MTX**
Primary objectives	- To study in patients with severe RA, the daily practice efficacy and effectiveness of a modified COBRA slim (without SSZ and with half dose steroids) scheme vs. a COBRA classic scheme (15 mg MTX) and a modified COBRA avant-garde scheme (Leflunomide instead of SSZ and half dose steroids). - To study in patients with less severe RA, the daily practice efficacy and effectiveness of a Tight Step Up regimen (with 15 mg MTX) vs. a modified Cobra slim scheme (without SSZ and with half dose steroids). - A superiority analysis will be performed: in the high risk arm, COBRA classic and COBRA avant-garde vs. COBRA slim and in the low risk arm, COBRA slim vs. Tight Step Up.

Outcome measures	- Primary outcome measures: proportion in remission at week 16, 52 and 104 - Secondary outcome measures: o efficacy at week 16, 52 and 104 using: ▪ Disease activity: proportion EULAR responders ▪ Proportion of patients in remission according to the SDAI (score ≤ 3,3). ▪ Proportion of patients in remission according to the CDAI (score ≤ 2,8). ▪ Proportion of patients in remission according to the preliminary Boolean ACR/EULAR criteria. ▪ Proportion of patients in remission according to DAS28CRP <2.4 ▪ Functionality: proportion CM HAQ responders and proportion HAQ = 0 ▪ X-ray (Sharp Vanderheijde score) (w28, 52 and 104) o Effectiveness at week16, 52 and 104 using: ▪ Proportion treatment failures due to efficacy/effectiveness problems (only failure due to toxicity at week 16) ▪ Proportion with unplanned treatment changes ▪ Proportion lost of follow up ▪ Total cumulative steroid dose/mean steroid dose per day ▪ Proportion started on biologics (not at week 16) o Safety: number and type of (serious) adverse events. o Other outcome measures: Additional questionnaires as described in the flow chart.

List of Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	ALanine aminoTransferase
Anti CCP antibody	anti-Cyclic Citrullinated Peptide antibody
AST	ASpartaat-aminoTransferase
CM HAQ difference	Clinically Meaningful HAQ difference
CME	Centrum Menselijke Erfelijkheid
CNS	Central Nerveous System
COBRA	COmbinatie therapie Bij Reumatoïde Artritis
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
DAS28	Disease Activity Score based on the 28 joint count
DMARD	Disease Modifying Anti Rheumatic Drug
EC	European Commission
eCRF	electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
ET	Early Termination
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GH	General Health
GI	Gastro Intestinal
GOT	Glutamate Oxaloacetate Transaminase
GPT	Glutamate Pyruvate Transaminase
HAQ	Health Assessment Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethical Committee
IM	Intra Muscular
IPQ	Illness Perception Questionnaire
IRB	Institutional Review Board
MACTAR questionnaire	McMaster Toronto Arthritis patient preference
MFI20 questions	Multidimensional Fatigue Inventory based on 20
mg	Milligrams
MTX	Methotrexate
NSAID	Non Steroidal Anti Inflammatory Drug
QOL	Quality Of Life
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SC	Sub Cutaneous
SF36	Short Form 36
SJC	Swollen Joint Count
SPSS	Statistical Package for the Social Sciences
SSL	Social Support List
SSZ	Sulfasalazine
TEN	Toxic Epidermal Necrolysis
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
UCL	Utrecht Coping List
ULN	Upper Limit of Normal
UZ	University Hospital
VAS	Visual Analog Scale

1. Study title

CareRA: a 2 year prospective multicentre randomised controlled trial comparing effectiveness in daily practice of different treatment strategies for early RA.

2. Rationale and introduction

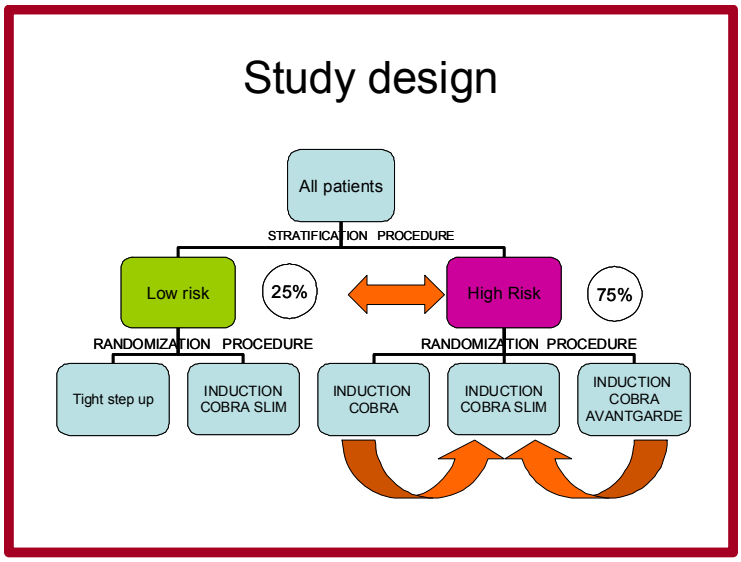
The COBRA trial was a milestone in the development of the present treatment paradigm for Rheumatoid Arthritis (RA)[1]. This study introduced the principle of fast remission induction by means of a combination of standard disease modifying antirheumatic drugs (DMARD: methotrexate (MTX) plus sulphasalazine) and a step down bridge therapy with high dose steroids in early Rheumatoid Arthritis (RA). A step down strategy proved more effective than a more conservative step up approach with a single DMARD, without increased side effects or costs. Although meanwhile the importance of early intensive treatment has been confirmed and emphasized in numerous publications[2;3;4] there seems to be a discrepancy between theoretical acceptance and practical implementation of this strategy in the rheumatologic community[5]. The most important reason why rheumatologists do not prescribe the COBRA scheme in daily practice seems to be concern about their patient's opinion on the complexity of the scheme and the large amount of drugs they have to take. In addition, patients dislike corticosteroids and prefer newer drugs such as anti-TNF agents, but this unfavorable perception seems to improve after steroid use[6]. Rheumatologists have also doubts about the initial high dosage of steroids, the relatively low dose of MTX (7.5 mg per week) and the use of sulphasalazine as maintenance therapy in the original COBRA scheme[5]. In a previous study we showed the feasibility of using a step down strategy based on the original COBRA scheme for early RA treatment in daily practice[7]. In our study with an adapted COBRA regimen we increased the MTX dose to 15 mg per week and randomized patients to maintenance therapy with either sulphasalazine (SSZ) or MTX[7]. The higher MTX dosage did not cause more side effects and MTX proved to be the most effective maintenance therapy.

In the present randomized controlled trial we will stratify patients according to their disease severity based on a theranostic model including classical prognostic factors such as the presence of rheumatoid factor, anti-CCP antibodies, erosive status and baseline disease activity. In RA patients with a low risk of radiographic progression of a severe disease course, we compare a modified version of the COBRA regimen including lower dosages of steroids and without sulphasalazine (COBRA slim), with a generally accepted step up treatment. In the group of early RA patients with a high risk of severe disease we compare the original COBRA regimen (COBRA classic) with modified COBRA versions including a MTX-low steroid schedule (COBRA slim) and a combination of MTX with leflunomide instead of SSZ (COBRA avant-garde).

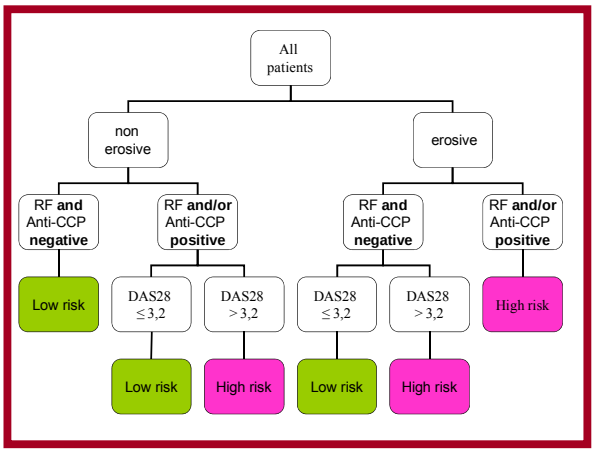
3. Study design

3.1. Overall design

In this prospective multicentre randomised controlled trial of **2-year** duration, **400** patients with early active RA (≤1 year), previously untreated with DMARDs, will be stratified according to their disease severity and subsequently randomly assigned to different treatment strategies (see flow chart).



Disease severity will be determined according to a flow chart based on Rheumatoid Factor and anti-CCP antibody status, erosive disease or not and disease severity. The different randomization options will depend on disease severity (see diagram below).



Patients with severe disease

Induction phase:

Patients with severe RA will be randomized to three different remission induction regimens including steroids. In all treatment arms patients will initially receive a high dose of oral steroids that will be tapered down rapidly on a weekly basis according to the timelines of the original COBRA trial (cfr. infra) and from week 28 onwards steroids will be further tapered down over 6 weeks till discontinuation. In two treatment arms patients will receive initial DMARD combination therapy.

- Group 1a: **COBRA classic**
  - MTX 15 mg
  - Sulphasalazine 2000 mg
  - Step down steroid full dose: 60-40-25-20-15-10-7.5 mg prednisone, each for 7 days

- Group 2a: **COBRA slim**
  - MTX 15 mg
  - Step down steroid half dose: 30-20-12.5-10-7.5-5 mg prednisone, each for 7 days

- Group 3a: **COBRA avant-garde**
  - MTX 15 mg
  - Leflunomide 10 mg
  - Step down steroid half dose: 30-20-12.5-10-7.5-5 mg prednisone, each for 7 days

From week 28 onwards steroids will be tapered down on a weekly basis by leaving out one day dose of steroids each week over a period of 6 weeks, till discontinuation.

Maintenance phase:

After the induction phase, from week 40 onwards, the maintenance phase starts. Patients will receive a single DMARD maintenance therapy with either MTX or leflunomide, except in case the investigators feels it is not possible to switch back to mono-therapy due to recent adaptations to the treatment scheme.

At week 40, patients in group 3a will be randomly assigned to maintenance therapy with either MTX or leflunomide if their disease activity is acceptably low (DAS 28 CRP $\leq$ 3.2). To evaluate the DAS 28 CRP at this time point, it is allowed to use blood samples taken within a timeframe of five days of the visit date.
Patients in group 1a and 2a will continue MTX as maintenance therapy if their disease activity is acceptably low (DAS 28 CRP $\leq$ 3.2).
The maintenance dose of MTX is minimally 15 mg per week and the minimum maintenance dose of leflunomide is 20 mg daily. Further reduction of DMARD dosages during study will only be allowed in case of toxicity.

If at the end of the induction phase (week 40) disease activity is not acceptably low (DAS28 >3.2), patients can continue in the induction phase depending on the number of treatment adjustments already made (section 3.2).

In case no previous treatment adaptations have been made, treatment adjustments as described in section 3.2 can be made between week 40 and week 52, preferably 1 adjustment at week 40 and if necessary another at week 44. The final evaluation of these interventions will take place at week 52. When disease activity is not acceptably low (DAS28>3.2) at week 52, patients are considered treatment failures, if the disease activity is below or equal to 3.2, patients will continue the study in maintenance phase.

In case only one treatment adjustment was done before week 40 one extra adaptation can be made as described in section 3.2 of the protocol. These patients will be evaluated at week 48. If disease activity is not acceptably low (DAS28>3.2) at that time point, the patients will be considered a treatment failure. Otherwise if DAS28 ≤ 3.2 patients will continue the study in maintenance phase.

If at the end of the induction phase disease activity is not acceptably low (DAS28 > 3.2) and 2 previous treatment adjustments were made, patients will be considered as treatment failures.

Once patients enter the maintenance phase treatment adjustments from w52 onwards will be at the discretion of the physician according to good clinical practice. This means that there is no more restriction concerning treatment adaptations and the rule that 2 adaptations would lead to a treatment failure is no longer applicable.

Patients with less severe disease

Patients with less severe RA will be randomized to either a classic step up regimen without steroids, or a remission induction regimen including steroids which will be tapered down according to the timelines of the original COBRA trial (see above).

- Group 1b: **Tight Step Up**
  - MTX 15 mg
  - No additional oral steroids allowed

- Group 2b: **COBRA slim**
  - MTX 15 mg
  - Step down steroid half dose: 30-20-12.5-10-7.5-5 mg prednisone

3.2.Treatment adjustments during the induction phase of the study

If patients fail to respond (DAS 28 CRP > 3.2) programmed treatment adjustments will be made from 8 weeks of treatment onwards, if desirable and feasible.

The first step in all groups is a MTX dose increase to 20 mg per week.

If patients fail to respond (DAS 28 CRP > 3.2) after the first adjustment, further adjustments will be made from 8 weeks after the first adjustment onwards (except for w40), if desirable and feasible.

The second step in group 1a is a sulphasalazine dose increase to 3g.

The second step in group 1b, 2a and 2b is to add leflunomide 10 mg.

The second step in group 3a is a leflunomide dose increase to 20 mg.

An intramuscular depot-corticoid injection is allowed together with these treatment adjustments, but not within 4 weeks preceding week 16, 28, 40 and week 52 visits.
As an alternative an oral bridging scheme could be considered, after discussion with the coordinating investigator (.Prof. Dr. P. Verschueren, 016 342541, patrick.verschueren@uz.kuleuven.ac.be)

Gewijzigde veldcode

Intra-articular corticosteroids are allowed maximally once every 8 weeks but not within 4 weeks preceding week 16, 28, 40 and week 52 visits.

3.3.Treatment failure during study

Treatment failures during the study are defined as failing to respond to the effectiveness criteria or as failing to complete a prescribed treatment arm (e.g. toxicities).
If during the induction phase patients fail to respond (DAS 28 CRP > 3.2) even after two predefined treatment adjustments, they will be considered treatment failures from week 24 onwards.
In this case anti-TNF combined with MTX will be the treatment of choice.
Patients not qualifying the reimbursement criteria for anti-TNF agents will be registered and followed up separately.
Patients who are considered treatment failure will be asked to return for a week 28, week 52, week 78 and/or week 104 visit depending on the time point in the trial the treatment failure is reached.
For all patients who failed the treatment (due to effectiveness or toxicity) a strategy failure/study completion page will be completed at the time of failure and they will be followed up as described above.

3.4.Treatment toxicity during study

General rule for combined DMARD treatment:

If AST or ALT is > 2 times but ≤ 3 times the upper limit of the normal range (ULN) in patients receiving combined DMARD treatment, the first measure will be to discontinue leflunomide or sulphasalazine treatment.
Re-evaluation of the blood tests will be done after two weeks.

In case of persistent liver disturbances, MTX will be tapered according to schedule and a new re-evaluation of the liver function will be scheduled. If after this, liver function is not recovered, this will be considered a treatment failure (see section 3.3). If the liver function is recovered or recovering MTX should be reintroduced within 4 weeks, other DMARDs must be reintroduced gradually within 8 weeks. In case not all medication can be reintroduced this will be considered a treatment failure.
In case of normalization of the liver function after two weeks, leflunomide or sulphasalazine can be re-introduced.

Toxicity of MTX in monotherapy:

General rule: dose reduction below 7.5mg for more than 4 weeks will be considered a treatment failure.

Dosage reduction:

- in case of gastrointestinal side effects, ulcerative stomatitis or CNS side effects: Dose reduction to ≥ 7.5mg (prior switch to IM/SC is preferred in case of GI side effects, ulcerative stomatitis)
- if AST or ALT > 2 times but ≤3 times ULN:
    - reduce by at least 50% to ≥ 7.5mg/week
    - if after 2 weeks AST or ALT are ≤ 2times ULN, MTX can be maintained at the lower dose or increased gradually up to a maximum of 20mg/week (rate 2.5mg every 2-4 weeks)
    - if AST or ALT are persistently >2 times ULN: discontinuation of MTX

- if AST or ALT > 3 times ULN:
    - discontinue MTX for 2 weeks
    - if after 2 weeks AST or ALT are ≤ 2 times ULN, MTX can be reintroduced at a lower dose or increased gradually up to a maximum of 20mg/week (rate 2.5mg every 2-4 weeks)
    - if AST or ALT persistently >2 times ULN: discontinuation of MTX

- Haematological toxicity: according to the decision of the treating physician
- Renal insufficiency: according to the decision of the treating physician
- Presumed pulmonary toxicity: discontinuation (treatment failure)
- Serious infections: temporary discontinuation for not more than 4 weeks is allowed

Toxicity of leflunomide in monotherapy:

- in case of diarrhoea or other subjective side effect:
    - dose reduction to 10 mg per week is allowed
- if AST or ALT is > 2 times but ≤3 times ULN:
    - reduce leflunomide to 10 mg/d
    - if after 2 weeks AST or ALT are ≤ 2 times ULN, leflunomide can be maintained at the lower dose or increased up to 20mg/d

    - if AST or ALT persistent >2 times ULN: discontinuation and wash out procedure
- if AST or ALT is > 3 times ULN:
    - discontinue leflunomide for 2 weeks
    - if after 2 weeks AST or ALT are ≤ 2 times ULN, leflunomide can be started again at 10 mg/d and later increased to 20mg/d
    - if AST or ALT are persistently >2 times ULN: discontinuation and wash out
- Haematological toxicity: according to the decision of the treating physician
- Renal insufficiency: according to the decision of the treating physician
- Ulcerative stomatitis or presumed Stevens-Johnson syndrome or TEN (toxic epidermal necrolysis): discontinuation and wash out (treatment failure)
- Presumed pulmonary toxicity: discontinuation and wash out (treatment failure)
- Serious infections: temporary discontinuation of not more than 4 weeks is allowed

Typical toxicity of sulphasalazine in combination therapy:

Typical cutaneous allergic reaction to sulphasalazine: discontinuation (treatment failure for the effectiveness evaluation)

4. Objectives

To study in patients with severe RA, the efficacy and effectiveness of a classic COBRA scheme (with 15mg MTX) versus two modified COBRA schemes respectively “slim” (without SSZ and with half dose steroids) and “avant-garde” (leflunomide instead of SSZ and half dose steroids) in daily practice.

To study in patients with less severe RA, the daily practice efficacy and effectiveness of a Tight Step Up regimen (with 15mg MTX) versus a modified COBRA slim scheme (without SSZ and with half dose steroids).

A superiority analysis will be performed: in the high risk arm, COBRA classic and COBRA avant-garde vs. COBRA slim and in the low risk arm, COBRA slim vs. Tight Step Up.

5. **Time schedule**

End point visits | Optional visits in case of not reaching the target and recent treatment adjustment or side effects

	Screen	BL	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w65	w78	w91	w104
Informed consent	X																		
Inclusion/Exclusion criteria	X																		
RF and anti-CCP	X														X				X
X-ray (Sharp Vanderheijde score)	X								X						X				X
Randomization procedure		X																	
Concommitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events / Serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TJC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SJC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard blood sample*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum and urine sample for storage**		X	X	X		X			X			X			X				X
Blood sample for genetics***		X																	
DAS28CRP / ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS GH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS pain		X		X		X			X			X			X	X	X	X	X
VAS fatigue		X		X		X			X			X			X	X	X	X	X
HAQ Questionnaire		X		X		X			X			X			X	X	X	X	X
Employment status before disease onset	X																		
Current employment status	X					X									X				X
Perception Steroids Questionnaire	X					X									X				
Educational level assessment		X																	
SF36 Questionnaire		X				X									X				X
RA QOL Questionnaire		X				X									X				X
IPQ		X				X									X				X
Social Support Questionnaire		X				X									X				X
MFI20 Fatigue Questionnaire		X				X									X				X
Pittsburgh Sleep Quality Questionnaire		X				X									X				X
Coping (UCL) Questionnaire		X				X													
Satisfaction Questionnaire															X				X

*Standard blood sample: ESR, ESR, complet, GOT, GPT and serum creatinin
**Serum and urine sample for storage in selected sites only
***Blood samples for genetics only in case of separate patient informed consent

A maximum of 4 weeks is allowed and a minimum of 1 day is required between screening and baseline visit (w0). In case a baseline visit is done within 5 days of screening, the results from the screening blood test can be re-used if no change is expected by the investigator.

For key visits (underlined) a time window of one week before and one week after the target date is accepted until week 52.
After week 52 a time window of two weeks before and two weeks after the target date is accepted.

At baseline (w0) a list with target dates (+/- window) for each follow up visit will be created.

6. Study population

6.1. Number of patients and assignment to treatment groups

A total of **400** patients are planned to be included in this study.
Patients with severe RA will be randomly assigned to one of three treatment groups of **100** patients each according to a 1:1:1 ratio. Patients with less severe RA will be randomly assigned to one of two treatment groups of **50** patients each according to a 1:1 ratio.
At randomization, subjects will be stratified according to their erosive status.

6.2. Inclusion criteria

Patients enrolled in the study must meet the following inclusion criteria:

- Age 18 years and older
- Diagnosis of RA as defined by the 1987-revised ACR classification criteria or the new ACR/EULAR2010 criteria for early RA
- Early RA defined by a disease duration ≤ 1 year
- Use a reliable method of contraception for women of childbearing potential
- Able and willing to give written informed consent and to participate in the study

6.3. Exclusion criteria

Patients will be excluded from participating in the study if they meet any of the following exclusion criteria:

- Previous treatment with methotrexate or leflunomide
- Previous treatment with cyclophosphamide, azathioprine or cyclosporine
- Previous treatment with sulphasalazine for more than 3 weeks
- Previous treatment with hydroxychloroquine for more than 6 weeks
- Previous treatment with oral corticosteroids at a daily dosage of more than 10 mg prednisone equivalent within 4 weeks before baseline
- Previous treatment with oral corticosteroids at a daily dosage equal to or less than 10 mg prednisone equivalent within 2 weeks before baseline
- Previous treatment with oral corticosteroids for more than 4 weeks within 4 months before screening
- Previous treatment with intra-articular corticosteroids within 4 weeks before baseline
- Previous treatment with an investigational drug for the treatment/prevention of RA
- Contraindications for corticosteroids
- Contraindications for methotrexate, sulphasalazine or leflunomide

        - known chronic hepatic disease (alcoholic, fibrosis, …)
        - known pulmonary interstitial disease or fibrosis
        - known chronic renal failure
        - history of malignant neoplasm within 5 years
        - hematologic problems at the discretion of the investigator
- Psoriatic Arthritis
- Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study
- Pregnancy, breastfeeding or no use of a reliable method of contraception
- Alcohol or drug abuse

6.4. Concomitant medication

- An extensive list of concomitant medication is recorded at baseline
- The use of NSAIDs should be recorded for effectiveness evaluation
- Paracetamol is allowed as long as it is recorded for effectiveness evaluation
- All study patients must receive oral folic acid supplements of minimally 1mg daily as well as Calcium and vitamin D (minimal 1000 mg/800IU daily).
- All changes in concomitant medication should be registered

7. **Outcome measures**

7.1. Primary outcome measures

- Proportion in remission (DAS28CRP < 2.6) at 16 weeks
- Proportion in remission (DAS28CRP < 2.6) at 52 weeks
- Proportion in remission (DAS28CRP < 2.6) at 104 weeks

7.2. Secondary outcome measures

Efficacy at 16 weeks, 52 weeks and 104 weeks:

- Disease activity:
  - Proportion good EULAR responders
  - Proportion of patients in remission according to the SDAI (score ≤ 3,3).
  - Proportion of patients in remission according to the CDAI (score ≤ 2 ,8).
  - Proportion of patients in remission according to the preliminary Boolean ACR/EULAR criteria.
  - Proportion of patients in remission according to DAS28CRP <2.4
- Functionality:
  - Proportion CM HAQ responders (delta > 0,22)
  - Proportion HAQ = 0
- X-ray (Sharp Vanderheijde score) (w28, 52 and 104)

Effectiveness at 16weeks, 52 weeks and 104 weeks:

- Proportion of treatment failures due to efficacy/effectiveness problems (only failure due to toxicity at week 16)
- Proportion with unplanned treatment changes (steroids and DMARDs)
- Proportion lost from follow up
- Total cumulative steroid dose / mean steroid dose per day
- Proportion started on biologics (not at week 16)

Safety: number / type of (serious) adverse events (see appendix 1)

7.3.Other outcome measures

- Recruitment analysis on all consecutive early RA patients
  - Proportion qualifying but unwilling to participate
  - Proportion qualifying but contra-indication
  - Proportion screen failures
  - Proportion in other trials
- Sensitivity analysis comparing the treatment response in patients fulfilling the ACR 1987 classification criteria for RA with those fulfilling the 2010 ACR/EULAR RA classification criteria
- Perception about steroids at baseline, week 16 and week 52
- Coping (UCL) at baseline and week 16
- Social support questionnaire at baseline (w0), week 16, week 52 and week 104
- RA QOL questionnaire at baseline, week 16, week 52 and week 104
- SF36 questionnaire at baseline, week 16, week 52 and week 104
- IPQ at baseline, week 16, week 52 and week 104

- Employment status at baseline, week 16, week 52 and week 104
- Patient satisfaction questionnaire at week 52 and 104
- MFI 20 fatigue questionnaire at baseline, week 16, week 52 and week 104
- Pittsburgh Sleep Quality Questionnaire at baseline, week 16, week 52 and week 104
- "Patient preference survey" before and during the study (cfr. Goekoop)
- "Doctors preference survey" before and during the study (cfr. Van Tuyl)

8. Study duration

This study has a duration of maximally 108 weeks (104 weeks of treatment and a maximal interval of 4 weeks between screening and baseline (w0)

9. Enrolment period

The enrolment period will be from 2008-06/2013.

10. Number of investigative sites

- Department of Rheumatology, University Hospital Leuven
- Cooperating Rheumatology Practices: cfr. supra.

11. Clinical Evaluation

11.1. Screening

A signed informed consent form must be obtained from each patient prior to any study-related procedure being performed. All test results and assessments required to establish eligibility of the patient must be obtained prior to enrolment and prior to dispensation of the medication.

The following are required at screening:

- signed informed consent form
- assessment of inclusion/exclusion criteria
- RF and anti-CCP
- X-ray (Sharp Vanderheijde Score)
- Concomitant Medication
- TJC, SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- Determination of the educational level
- Evaluation of employment status before onset of disease
- Current employment status / participation
- Perception Steroids (Questionnaire)

11.2. Baseline (w0)

The following are required at Week 0 visit:

- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine (in case screening blood samples were taken within 5 days, these values can be used).
- DAS28CRP/ESR
  (in case screening blood samples were taken within 5 days, these values can be used)
- VAS GH
- VAS pain and fatigue
- HAQ questionnaire
- SF36, RA QoL, IPQ, social support (SSL), fatigue (MFI-20), sleep quality (Pittsburgh Sleep Quality Questionnaire)
- Coping (UCL) questionnaire
- Serum and urine storage in selected sites only (in case the baseline visit will be done within 5 days from screening, these samples can be collected at screening)
- Genetic sample for consenting patients only (in case the baseline visit will be done within 5 days from screening, these samples can be collected at screening)

11.3. Week 4

The following are required at Week 4:

- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- Serum and urine storage in selected sites only

11.4. Week 8 and week 40, 65, 78 and 91

The following are required at Week 8, 40, 65, 78 and 91 visits

- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- VAS pain and fatigue
- HAQ questionnaire

- Serum and urine storage in selected sites only (only week 8)

11.5. Week 28

The following are required at week 28:

- X-ray (Sharp Vanderheijde Score)
- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- VAS pain and fatigue
- HAQ questionnaire
- Serum and urine storage in selected sites only

11.6. Endpoint Visits (week 16, week 52 and week 104)

The following are required at **week 16**:

- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- VAS pain and fatigue
- HAQ questionnaire
- Current employment status / participation
- Perception Steroids (Questionnaire)
- SF36, RA QoL, IPQ, social support (SSL), fatigue (MFI-20), sleep quality (Pittsburgh Sleep Quality Questionnaire)
- Coping (UCL) questionnaire
- Serum and urine storage in selected sites only

The following are required at **week 52**:

- RF and anti-CCP
- X-ray (Sharp Vanderheijde Score)
- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- VAS pain and fatigue
- HAQ questionnaire
- Current employment status / participation
- Perception Steroids (Questionnaire)

- SF36, RA QoL, IPQ, social support (SSL), fatigue (MFI-20), sleep quality (Pittsburgh Sleep Quality Questionnaire)
- Satisfaction questionnaire
- Serum and urine storage in selected sites only

The following are required at **week 104**:

- RF and anti-CCP
- X-ray (Sharp Vanderheijde Score)
- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH
- VAS pain and fatigue
- HAQ questionnaire
- Current employment status / participation
- SF36, RA QoL, IPQ, social support (SSL), fatigue (MFI-20), sleep quality (Pittsburgh Sleep Quality Questionnaire)
- Satisfaction questionnaire
- Serum and urine storage in selected sites only

In case of not reaching the target and recent treatment adjustment or in case of side effects the following optional visits can be performed: Week 12, week 20, week 24, week 32, week 36, week 44, week 48.

The following are required at these optional visits:

- Concomitant medication.
- Side Effects
- TJC and SJC
- Standard blood sample: ESR, CRP, complet, GOT, GPT and serum creatinine
- DAS28CRP/ESR
- VAS GH

11.7. Strategy failures

In case of strategy failure, data from the visit at which the decision is taken to consider the strategy as ineffective will be recorded. Radiological evaluation is required in case of strategy failure when no radiograph is available within the last 3 months preceding the strategy failure visit or expected according to the protocol within 3 months.
Evaluation of RF and CCP positivity are only required when the strategy failure visit is a w52 or a w104 visit.
Also in case of strategy failure patients will be asked to return for a week 28, week 52, week 78 and/or week 104 visit depending on the time point in the trial the treatment failure is reached.

12. Study discontinuation

The study may be discontinued by the organizer in case of safety concerns or major logistic problems.

13. Withdrawal of patients

Any patient may withdraw from the study for any reason at any time. The investigator may withdraw any patient from the study if it is not in the patient's best interest to continue.

When a patient withdraws or is withdrawn from the study, regardless of the reason, the date of withdrawal and the reason for termination should be documented on the strategy failure/completion page. To the extent possible all evaluations as required for a strategy failure will be recorded: radiological evaluation in case no radiograph is available within the last 3 months preceding withdraw and evaluation of RF and CCP positivity. Every effort should be made to determine the reason why patients fail to return for the necessary visits or withdraw from the study. If patients cannot be reached by phone, a letter should be sent requesting that contact will be made with the investigator to confirm the reason for withdrawal from the study.

14. Informed Consent

Each patient must provide informed consent in order to enrol in the study. The informed consent process will be conducted per institutional protocol and in compliance with applicable IEC and regulatory requirements.

There will be a separate informed consent form for patients not willing to participate to the medication study but prepared to provide demographical data for statistical comparison between participants and non-participants.

A separate informed consent form must be signed by patients prepared to give a blood sample for genetic analysis.

15. Patient randomisation

Each clinical site will be assigned a 3 digit site number, the patient numbers will start with this site number followed by a 3 digit patient number starting with 001. Randomisation will be done within the e-platform after confirmation of the in and exclusion criteria.

16. Laboratory Tests

A standard blood sample will be performed. The testing will be done by an accredited laboratory. The laboratory tests are as follows: ESR, CRP, complet, GOT, GPT and serum creatinine. Moreover extra serum and urine samples will be collected at each study visit for future scientific analyses.

At baseline a blood sample for genetic study will be taken only in patients prepared to sign a separate informed consent form. Genetic extractions and storage will be done by the CME, University Hospitals Leuven until further analysis.

17. Safety

17.1. Definition of an adverse event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product. The occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
The investigator and/or his study team will examine any patient experiencing an AE as soon as possible. The investigator will do whatever is medically necessary for the safety and well-being of the patient.

Severity Grading for Adverse Events:
Severity should be graded into one of the three classes which describe the clinical severity of the event as it occurred:

- Mild (does not interfere with daily living)
- Moderate (somewhat interferes with daily living or medications needed to relieve event)
- Severe (incapacitating)

Laboratory Abnormalities:
The investigator must assess the clinical significance of all abnormal laboratory values as defined by the compendium of normal values for the reference laboratory. Any clinically significant abnormalities should be investigated.
Collecting and Reporting Adverse Events:
Patients will be asked at each visit about the occurrence of any adverse events. Adverse events will not be collected or evaluated beyond the patient's final study visit. Adverse events should be followed by the investigator until they have returned to baseline or stabilized.

17.2. Definition of a Serious Adverse Event

The definition of a Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Fatal, resulting in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

In addition, important medical events that not fulfil above criteria may be considered Serious Adverse Events when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Any SAE that occurs during this study must be reported immediately. After completion of the seriousness criteria in the eCRF a SAE-form will automatically appear and should be completed by the investigator. This SAE reports will then be electronically signed and automatically e-mailed to the Department of Rheumatology of the University

Hospitals Leuven. The investigator must complete this form within 24 hours after becoming aware of the SAE.
Follow-up information must be submitted promptly by completing a follow up SAE form, which will be submitted by e-mail. The coordinating physician is available to provide medical guidance regarding SAE reporting.

17.3. Safety committee

A safety committee is installed to regularly review the safety data for the trial. The safety committee acts independently from the steering committee, and consists of 3 members not participating in the trial: 2 rheumatologists and 1 internal medicine specialist.
On a regular basis, after reviewing the safety data, they will give advice to the steering committee.

18. Obligations of the investigator

The investigator must comply with all applicable regulations. In addition, the investigator must follow local and institutional requirements pertaining, but not limited, to clinical research, informed consent and IRB/IEC regulations. The department of Rheumatology of the University Hospitals Leuven will provide notification to the investigators of protocol and amendment approvals by regulatory authorities, if applicable.

Except where the investigator's signature is specifically required, it is understood that the term "investigator" as used in this protocol and protocol related documents refers to the investigators and/or appropriate study personnel that the investigators designates to perform a certain duty. The investigator is ultimately responsible for the conduct of all aspects of the study.

19. Compliance with Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice as required by the 1997 International Conference on Harmonization (ICH) Guideline on Good Clinical Practice (ICH E6) and the European Directive 2001/20/EC.

The investigator at each clinical site must sign the Protocol Signature Page.

20. Compliance with the Declaration of Helsinki

This study will be conducted in accordance with ethical principles as described in the Declaration of Helsinki.

21. Institutional Review Board/Institutional Ethics Committee

Prior to enrolment of patients into this study, the final protocol, informed consent form (ICF) and any patient recruitment materials will be submitted to, and reviewed and approved by an Institutional Ethics Committee (IEC).

Any necessary amendments to the protocol and/or ICF will be prepared by the Rheumatology Department of the University Hospitals of Leuven and provided to the investigator for submission to the IRB/IEC.

22. Informed Consent Process

The investigator will choose patients in accordance with eligibility criteria. The investigator will not exercise selectivity so that bias is prevented. All patients must sign an informed consent form that complies with the requirements of ICH E6 before entering the study.

Prior to the study, patients will receive a comprehensive explanation of the proposed treatment including the nature and risks of the study, alternate therapies, any known adverse events, the medicinal product, and the other elements that are part of proper obtaining informed consent. Patients will be allowed sufficient time to consider participation in the study, after having the nature and risks of the study explained to them.

By signing the informed consent form, the patient agrees to complete all evaluations required by the study, unless the patient withdraws voluntarily or is terminated from the study for any reason.

23. Data acquisition

For this study an electronic case report form (eCRF) will be used. Study monitors (CRA) will review the eCRFs for completeness and accuracy by comparing them to the source documents at the clinical study site.

24. Source Documents

Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator will maintain complete and accurate documentation for the study.

As defined in section 1.52 of the ICH Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, ...)
All source documents and laboratory reports will be reviewed by the clinical team to ensure that they are accurate and complete.

25. Retention of Documentation

All documents related to the study must be kept as described in the ICH-GCP guidelines.

26. Confidentiality

The study protocol and other written materials provided by the Department of Rheumatology of the University Hospitals of Leuven and documentation, data and other information generated as part of this study will be held in strict confidence by the investigator and site staff. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Department of Rheumatology of the University Hospitals of Leuven.

27. Deviations from protocol

In general no deviations to the protocol will be granted, unless there is an agreement and approval of the steering committee after discussion with the investigator.

28. Study monitoring

Prior to the treatment on a patient the monitor shall ensure that the investigator understands all requirements of the protocol and his/her regulatory responsibilities as an investigator. The monitor will visit each clinical study site at appropriate intervals to ensure compliance with the protocol, to verify accuracy, completeness and correctness of data.

29. Final Report from investigator

The coordinating investigator will write a final report after completion of the study in accordance with the EudraCT guidelines.

30. Publication

The results of the main study will be submitted for publication in a peer reviewed rheumatology journal. All centres will be entitled to one authorship for the publication of the week 16 and week 52 data, depending on the requirements and regulations of the journal. Authorships for all other publications will be depending on the contribution of an investigator to the manuscript and inclusion of patients. All investigators will be mentioned as members of the CareRA study group. Additional publications concerning study data will have to be approved by the CareRA study group.

31. Proposed analysis plan

A superiority analysis will be performed: in the high risk arm, COBRA classic and COBRA avant-garde vs. COBRA slim and in the low risk arm, COBRA slim vs. Tight Step Up. In collaboration with the department of biostatistics a power analysis was performed based on the primary outcome parameter in the high risk group: proportion of patients in remission at month 4. A total of 100 patients per treatment arm is required to show a statistical difference between COBRA classic or COBRA avant-garde and COBRA slim, with a power of 80% (Alpha 5%), starting from an estimated difference in effect size of 20%. The statistical analysis will be performed with SPSS 12 using parametric or non-parametric tests, depending on the distribution of the data.
An interim analysis will be performed on the week 16 and week 52 data of the total patient population.

32. Study Material

32.1. Resources for data analysis

As this is an investigator initiated trial, the Department of Rheumatology of the University Hospitals Leuven will provide the resources for data analysis.

32.2. Medication

The leflunomide for group 3a will be distributed by the Department of Rheumatology of the University Hospitals Leuven. Sanofi-Aventis will provide this medication without any charge. All other medication used in this study will be prescribed by means of pre-printed prescription forms, which will be provided by the Department of Rheumatology of the University Hospitals Leuven. The patient will collect this medication at the pharmacy as in normal daily practice.

Summary

Introduction

The last decades meant a revolution for the treatment of patients with early Rheumatoid Arthritis (RA). In the past, patients were treated conservatively and treatment was only intensified when disease escalated, leading to structural damage and functionality loss in many RA patients. Nowadays, it is clear that early, intensive treatment with a clear predefined treatment target leads to excellent clinical outcomes for the majority of patients with early RA. First of all, it is shown that the earlier the treatment is started in RA, the better outcome the patient has. However, no information on the current extent of treatment delay was available for Flanders before this thesis. Secondly, many attempts are made to tailor treatment to an individual patient based on prognostic factors, to improve further disease outcome such as structural damage. However, algorithms combining these prognostic factors to aid a physician in his treatment choice were not yet tested in daily practice. Thirdly, many intensive treatment options exist nowadays to treat a patient with early RA. Yet, debate is ongoing on the exact content of this intensive treatment.

Objectives

The objectives of this research project were to determine:

1) the treatment delay, defined as the time between symptom onset and treatment initiation in Flanders
2) the reliability of classical prognostic factors in daily clinical practice
3) the optimal intensive treatment strategy for every patient with RA

Results

In chapter 1, we demonstrated that in Flanders only one on five of newly diagnosed RA patients are treated in a timely fashion. Patients expressing more severe disease characteristics at baseline seemed to present themselves earlier to the treating rheumatologist than those without. Moreover, a difference in treatment delay between the different types of rheumatology practices was found. Patients treated in academic and general hospitals showed longer treatment delays than those treated in private practices. Furthermore, patient-related delay

contributed the most to overall treatment delay in Flanders. Further research showed that aside of clinical characteristics, psychosocial factors also contributed to this patient-related delay. More research is needed to unravel the patient's help seeking behaviour.

In chapter 2, we firstly showed that composite algorithms using classical prognostic markers to predict structural damage in patients with early RA could not be reliably used in daily practice. No patients that developed rapid structural damage could be correctly identified by using these composite algorithms. Further in chapter 2, we showed that a combination of classical DMARDs with a GC bridging scheme seemed more effective than DMARD monotherapy in achieving higher remission rates and less radiographic progression after two years of treatment in our observational early RA cohort. Patients in this cohort were selected by the treating physician based on the presence of classical prognostic factors to receive a more conservative therapy if the RA profile of the patient seemed less severe at baseline. Hence, classical prognostic factors seem at the moment unreliable to base treatment choice upon in daily practice.

In chapter 3, we presented the results of the CareRA RCT, showing firstly that in patients with poor prognosis markers after 16 weeks of treatment DMARD combinations with a high or moderate dose glucocorticoid (GC) remission induction scheme were not superior to Methotrexate (MTX) only with a moderate dose GC remission induction scheme. The efficacy of the three compared treatment strategies was similar. Yet, the safety profile was more advantageous for MTX only with a moderate GC scheme. Furthermore, we showed that MTX monotherapy with a moderate dose GC remission induction scheme seems more efficacious than MTX monotherapy without GCs in patients presenting without poor prognosis markers after 16 weeks of treatment. Most remarkable was the comparable safety profile between both treatments. Lastly, we investigated the efficacy and safety in the CareRA trial after one year of treatment for both patients with or without poor prognosis. The results confirmed the findings at week 16.

The overarching conclusion regarding the third objective of this thesis is thus that MTX with an initial moderate dose glucocorticoid remission induction scheme seems to fit all patients with RA, with a high efficacy and acceptable safety profile.

Conclusion

Firstly, treatment delay is found to be too long in Flanders. Secondly, current classical biomarkers are not reliable in daily practice to guide treatment choice. Thirdly, MTX only combined with an initial moderate dose glucocorticoid remission induction scheme is very efficacious and safe for all patients with RA. We hope to have added essential evidence for an improved treatment outcome for every patient with RA with this thesis.

Samenvatting

Inleiding

De laatste decennia betekenden een revolutie in de behandeling van patiënten met beginnende Rheumatoïde Arthritis (RA). In het verleden werden deze patiënten voornamelijk conservatief behandeld. De behandeling werd pas opgedreven naarmate de ziekte escaleerde met belangrijke structurele schade en verlies van functionaliteit als gevolg voor vele patiënten met RA. Tegenwoordig is het duidelijk dat vroege intensieve behandeling met een vooropgesteld behandelingsmikpunt leidt tot uitstekende klinische resultaten voor de meeste patiënten. Ten eerste is aangetoond dat hoe eerder de behandeling wordt opgestart bij een patiënt met vroege RA, hoe beter de resultaten zijn voor de patiënt. Er was echter voor aanvang van deze thesis geen informatie beschikbaar over de orde van grootte van de behandelingsvertraging in Vlaanderen. Ten tweede is onderzocht hoe betrouwbaar de op dit moment beschikbare prognostische factoren zijn voor het voorspellen van de ernst van de ziekte en de respons op behandeling bij de individuele patiënt om zo nefaste ziekteuitkomsten zoals structurele schade te vermijden. Algoritmen die deze klassieke prognostiche factoren combineren, om zo de arts bij te staan in zijn keuze van een behandeling waren nog niet getest in de dagelijkse praktijk. Ten derde bestaan er vele intensieve behandelingsopties bij beginnende RA. Wat de exacte inhoud van deze intensieve behandeling is, is nog steeds voer voor debat.

Doelstellingen

De doelstellingen van dit onderzoeksproject zijn het bepalen van:

1) de behandelingsvertraging, gedefinieerd als de tijd tussen de aanvang van de symptomen en de start van de behandeling, specifiek in Vlaanderen
2) de betrouwbaarheid van klassieke prognostische factoren in de dagelijkse klinische praktijk
3) de optimale intensieve behandelingsstrategie voor elke patiënt met RA

Resultaten

In hoofdstuk 1 hebben we aangetoond dat in Vlaanderen slechts één op vijf van de nieuw gediagnosticeerde RA patiënten tijdig werd behandeld. Patiënten met ernstigere ziektekenmerken leken zich vroeger bij de behandelende reumatoloog te presenteren dan degenen zonder. Bovendien werd er een verschil in de vertraging op het starten van de behandeling gevonden tussen de verschillende vormen van reumatologie praktijken. Patiënten in de academische en algemene ziekenhuizen toonden langere vertragingen dan degene in privé-praktijken. Ook werd vastgesteld dat de aan de patiënt gerelateerde vertraging het meeste bijdroeg tot de totale behandelingsvertraging.

In hoofdstuk 2 bleek dat algoritmen samengesteld op basis van klassieke prognostische biomarkers om structurele schade te voorspellen bij patiënten met beginnende RA niet betrouwbaar kunnen worden gebruikt in de dagelijkse praktijk. Aan de hand van deze algoritmen konden geen patiënten die achteraf snelle structurele schade bleken te ontwikkelen, worden geïdentificeerd. Verder in hoofdstuk 2 hebben we aangetoond op basis van observationeel onderzoek dat een combinatie van klassieke antireumatica met een schema van glucorticoïden effectiever leek dan de conservatieve monotherapie na twee jaar behandeling. De behandelende arts selecteerde aan de hand van klassieke prognostiche factoren voor zijn patiënten met minder ernstige ziektekenmerken een meer conservatieve therapie. Patienten met een ogenschijnlijk gunstige prognose blijken dus toch minder goed geholpen te worden met een conservatieve therapie.

In hoofdstuk 3 rapporteren we de resultaten van de CareRA RCT, waarin we in de eerste plaats hebben vastgesteld dat, bij patiënten met markers van slechte prognose na 16 weken behandeling, DMARD combinaties met een remissie inductie schema startend bij een hoge of matige dosis glucocorticoïden (GC) niet superieur waren aan Methotrexate (MTX) met een remissie-inductie schema startend bij een matige dosis GC. De doeltreffendheid van de drie vergeleken behandelingsstrategieën was vergelijkbaar. Het veiligheidsprofiel was gunstiger

voor MTX met een matige dosis GC. Verder toonden we aan dat, bij patiënten zonder merkers van slechte prognose na 16 weken behandeling, MTX monotherapie met een remissie inductie schema startend bij een matige dosis GC effectiever leek dan MTX zonder GC. Het meest opvallende was het vergelijkbare veiligheidsprofiel tussen beide behandelingen. Tenslotte onderzochten we in de CareRA trial de doelmatigheid en veiligheid van intensieve therapieën na één jaar behandeling bij zowel patiënten met of zonder een slechte prognose. De resultaten bevestigden de bevindingen van week 16. De algemene conclusie van hoofdstuk drie luidt dan ook dat MTX met een remissie inductie schema startend bij een matige dosis GC past bij alle patiënten met RA, met een hoge werkzaamheid en aanvaardbaar veiligheidsprofiel.

Conclusie

Ten eerste is de vertraging alvorens te starten met een behandeling voor RA te lang in Vlaanderen. Ten tweede zijn de huidige klassieke prognostische biomarkers niet betrouwbaar voor het sturen van de behandelingskeuze in de dagelijkse praktijk. Ten derde is MTX gecombineerd met een remissie-inductie schema startend bij een matige dosis GC, zeer doeltreffend en veilig voor alle patiënten met beginnende RA. Met dit proefschrift hopen we bij te dragen tot een betere behandeling voor elke patiënt met beginnende RA.

Short curriculum vitae

Diederik De Cock was born on March 14th, 1987 in Leuven, Belgium. He was raised in the village of Tremelo, known for its local saint and most famous Belgian, Saint Damien of Molokai. He started his training in Biomedical Sciences at the Faculty of Medicine, Katholieke Universiteit Leuven, Belgium where he graduated cum laude in 2010 (Master in Biomedical Sciences) and cum laude in 2011 (Master in Management). In October 2011, he started his PhD in the department of Rheumatology under supervision of Prof. Dr. Patrick Verschueren and Prof. Dr. René Westhovens. He combined his PhD training with excellent tennis results. Between 2011 and 2015, Diederik won 12 tournaments under the supervision of his devoted manager François De Cock and his personal physical and mental trainer Annelies Vandendriessche. Especially the highly ranked tournament in Panorama, Overijse was a prestigious accomplishment. Furthermore, Diederik has been the criteriumleader Flemish Brabant Gentlemens 5 of 2013 and 2014 and won the Flemish Brabant 's master criterium in 2013 after a 4 hour marathon match against a motivated Syrian bloke from Dubai. Diederik is also a running and cycling enthousiast with outstanding perfomances such as climbing the Mont Aigual twice on bike; and performing the bike and run, Louvain la neuve – Leuven twice with his esteemed PhD colleague Sabrina Meyfroidt. Races such as the Corrida Leuven and 'De Loop zonder Dope' are also run with vigour. Aside from sports, Diederik also enjoys travelling with family and friends. His travels to China, Argentina, Sri Lanka and Oost-Zwevezele broadened his horizon and showed how lucky we are in gray and rainy Belgium.

List of publications

1. Verschueren, P.*, **De Cock, D.***, Corluy, L., et al (2015) Effectiveness of methotrexate with step down glucocorticoid remission induction (Cobra Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat to target approach: 1 year results of CareRA, a randomized pragmatic superiority trial. Submitted in the Lancet.
   * Verschueren P and De Cock D share a first co-authorship.

2. Meyfroidt, S., Stevens, J., De Lepeleire, J., Westhovens, R., **De Cock, D.**, Van der Elst, K., Vanhaecht, K., Verschueren, P. (2015). A general practice perspective on early rheumatoid arthritis management: a qualitative study from Flanders. The European Journal of General Practice – accepted 17 july 2015.

3. Van der Elst, K.*, **De Cock, D.***, Vecoven, E., Arat, S., Meyfroidt, S., Joly, J., Verschueren, P., Westhovens, R. (2015). Are illness perception and coping style associated with the delay between symptom onset and the first General Practitioner consultation in early Rheumatoid Arthritis management? An explorative study within the CareRA trial. Scandinavian Journal of Rheumatology 2015:1-8.
   *Van der Elst K and De Cock D share a first co-authorship.

4. **De Cock, D.**, Van der Elst, K., Meyfroidt, S., Verschueren, P.,Westhovens, R. (2015) The optimal combination therapy for the treatment of early rheumatoid arthritis. Expert Opinion on Pharmacotherapy, 16(11):1615-25.

5. Verschueren, P.*, **De Cock, D.***, Corluy, L., et al (2015) Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early Rheumatoid Arthritis: week 16 results from the randomized multicenter CareRA trial. Arthritis Research & Therapy, 17(1):97.
   * Verschueren P and De Cock D share a first co-authorship.

6. Meyfroidt, S., Hulscher, M., **De Cock, D.**, Van der Elst, K., Joly, J., Westhovens, R., Verschueren, P. (2015). A maximum difference scaling survey of barriers to intensive combination-treatment strategies with glucocorticoids in early rheumatoid arthritis. Clinical Rheumatology, 34(5):861-9.

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8. Verschueren, P*., **De Cock, D.***, Corluy, L., et al (2014). Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. Annals of the rheumatic diseases, 74(1):27-34.
   *Verschueren P and De Cock D share a first co-authorship.

9. Meyfroidt, S., van Hulst, L., **De Cock, D.**, Van der Elst, K., Joly, J., Westhovens, R., Hulscher, M., Verschueren, P. (2013). Factors influencing the prescription of intensive combination treatment strategies for early rheumatoid arthritis. Scandinavian Journal of Rheumatology, 43(4):265-72.

10. **De Cock, D.**, Vanderschueren, G., Meyfroidt, S., Joly, J., Van der Elst, K., Westhovens, R., Verschueren, P. (2013). The performance of matrices in daily clinical practice to predict rapid radiologic progression in patients with early RA. Seminars in Arthritis and Rheumatism, 43(5):627-31.

11. **De Cock, D.**, Vanderschueren, G., Meyfroidt, S., Joly, J., Westhovens, R., Verschueren, P. (2013). Two-year clinical and radiologic follow-up of early RA patients treated with initial step up monotherapy or initial step down therapy with glucocorticoids, followed by a tight control approach: lessons from a cohort study in daily practice. Clinical Rheumatology, 33(1):125-30.

12. **De Cock, D.**, Meyfroidt, S., Joly, J., Van der Elst, K., Westhovens, R., Verschueren, P., on behalf of the CareRA study group* (2013). A detailed analysis of treatment delay from the onset of symptoms in early rheumatoid arthritis patients. Scandinavian Journal of Rheumatology, 43(1):1-8.

13. Novaković, R., Cavelaars, A., Geelen, A., Nikolić, M., Altaba, I., Viñas, B., Ngo, J., Golsorkhi, M., Medina, M., Brzozowska, A., Szczecinska, A., **De Cock, D.**, Vansant, G., Renkema, M., Majem, L., Moreno, L., Glibetić, M., Gurinović, M., Van't Veer, P., de Groot, L. (2013). Review Article Socio-economic determinants of micronutrient intake and status in Europe: a systematic review. Public Health Nutrition 17(5):1031-45.

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- De Cock, D., Verschueren, P., Corluy, L., et al (2015) Remission induction with DMARD combinations and glucocorticoids is not superior to remission induction with MTX monotherapy and glucocorticoids: week 52 results of the high-risk group from the CareRA trial, **Oral presentation**: Belgian Congress of Rheumatology. Genk, Belgium, 23-25 September 2015.

- De Cock, D., Verschueren, P., Corluy, L. (2015) Low-risk patients also benefit from remission induction treatment in early Rheumatoid Arthritis: week 52 results from the CareRA trial. Belgian Congress of Rheumatology. Genk, Belgium, 23-25 September 2015.

- Verschueren, P., De Cock, D., Corluy, L., et al (2015) Remission induction with DMARD combinations and glucocorticoids is not superior to remission induction with MTX monotherapy and glucocorticoids: week 52 results of the high-risk group from the CareRA trial, **Oral presentation**: European Congress of Rheumatology EULAR. Rome, Italy, 10-13 June 2015.

- De Cock, D., Verschueren, P., Corluy, L. (2015) Low-risk patients also benefit from remission induction treatment in early Rheumatoid Arthritis: week 52 results from the CareRA trial, **Poster-guided tour**: European Congress of Rheumatology EULAR. Rome, Italy, 10-13 June 2015.

- De Cock, D., Van der Elst, K., Stouten, V., Peerboom, D., Meyfroidt, S., Joly, J., Westhovens, R., Verschueren, P. (2015). Symptom Onset and Help-seeking trajectory of patients with Rheumatoid Arthritis: vol. 54. Rheumatology 2015. Manchester, United Kingdom, 28-30 april 2015, i115, Abstract No. 168.

- De Cock, D., Verschueren, P., Corluy, L., et al. Associated with a glucocorticoid bridging scheme, methotrexate is as effective alone as in combination with other DMARDS for early rheumatoid arthritis, with fewer reported side effects: 16 weeks remission induction data from the CareRA trial **Oral Presentation**, Belgian Congress of Rheumatology, Brussels, Belgium, September 2014

- De Cock, D., Verschueren, P., Corluy, L., et al. Comparison of Mtx therapy with or without a moderate dose glucocorticoid bridging scheme in early rheumatoid arthritis patients lacking classical poor prognostic markers: week 16: results from the randomized multicenter CareRA trial **Poster Guided Tour.** Belgian Congress of Rheumatology, Brussels, Belgium, September 2014

- De Cock, D., Verschueren, P., Corluy, L., et al. Comparison of Mtx therapy with or without a moderate dose glucocorticoid bridging scheme in early rheumatoid arthritis patients lacking classical poor prognostic markers: week 16: results from the randomized multicenter CareRA trial **Poster Guided Tour.** EULAR 2014, Paris, France, June 2014.

- Verschueren, P., De Cock, D., Corluy, L. et al. Associated with a glucocorticoid bridging scheme, Methotrexate is as effective alone as in combination with other DMARDs for early rheumatoid arthritis, with fewer reported side effects: 16 weeks remission induction data from the CareRA trial. EULAR 2014, Paris, France June 2014.

- De Cock, D., Meyfroidt, S., Joly , J., Van der Elst, K., Westhovens R., Verschueren, P. on behalf of the CareRA study group. For Remission Induction with Glucocorticoid Bridging, Methotrexate Monotherapy Is As Effective As a Combination with Other Dmards, with Fewer Reported Side Effects: 4 Month Primary Outcome of Carera, a Randomized Induction Strategy and Treat to Target Trial in Early RA. **LATE BREAKING ABSTRACT.** ACR 2013. San Diego, USA, November 2013.

- De Cock, D., Meyfroidt, S., Joly , J., Van der Elst, K., Westhovens R., Verschueren, P. on behalf of the CareRA study group. Access to care: type of rheumatology practice influences treatment delay. International conference for rheumatology nurses. Rotterdam, The Netherlands, October 2013.

- De Cock, D., Vanderschueren, G., Lateur, L., Meyfroidt, S., Joly, J., Westhovens, R., Verschueren, P. Two year radiological follow-up of early rheumatoid arthritis patients treated with initial step up monotherapy or initial step down therapy with glucocorticoids, followed by a tight control approach. Belgian Congress of Rheumatology. Oostende, Belgium, September 2013.

- De Cock, D., Vanderschueren, G., Lateur, L., Meyfroidt, S., Joly, J., Westhovens, R., Verschueren, P. Performance of prediction matrices for rapid radiologic progression in daily practice. Belgian Congress of Rheumatology. Oostende, Belgium, September 2013.

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- De Cock, D., Vanderschueren, G., Lateur, L., Meyfroidt, S., Joly, J., Westhovens, R., Verschueren, P. Two year radiological follow-up of early rheumatoid arthritis patients treated with initial step up monotherapy or initial step down therapy with glucocorticoids, followed by a tight control approach. EULAR 2013. Madrid, June 2013.

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Abstracts as co-author are not listed.